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THE BIOLOGY OF THE CLINICAL PATHOLOGIST*

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The clinical pathologist is an animal of lowly origin and somewhat uncertain parentage. He had his origin as a biologic variant in response to an environmental demand. His development from a simple body with few and uncomplicated functions has been so rapid that in the life time of most of us we have seen his evolution into a complex creature with multitudinous functions and relationships. Because his evolution has been so rapid his adaptations have not been perfect and there are still evidences of maladjustment to environmental conditions. There has been the usual amount of variation in species brought about by differences in pressure of varying factors. There has been a loss here and a gain there in the constant attempt at adjustment. Some have fallen by the way side because of their inability to meet the rigorous conditions of existence. Some, who have survived, have so modified their characteristics that they closely resemble members of other families, and need to be carefully examined to determine their true character. Some have been fortunately situated and have flourished unchecked by unfavorable circumstances and stand out as examples of the finest type of development. And, then, as always, there is the occasional biologic sport which appears without known cause and refuses to be classified by any known rules into any known group.

Biologically, the clinical pathologist still shows many primitive characters and, in some respects, resembles the lower forms of animal life. Conversely, in his evolution, he has lost some of the capacities which were prominent in earlier days. For example,

*Presidential address read before the Ninth Annual Convention of the American Society of Clinical Pathologists, Detroit, Michigan, June 20–23, 1930.

while the ability to do work has increased, the ability to maintain normal nutrition has not kept pace and, in a medium weakened by competitive organisms of lower grade, he finds it difficult to maintain himself.

A comparison with one form of simple organism, with which you are all familiar, namely, the bacterium, will serve to illustrate the retention of some fundamental primitive characters.

Bacteria may be roughly divided into parasitic and non-parasitic organisms. So may clinical pathologists. Some of them maintain an independent existence by virtue of necessity; others, by choice. Some live at the expense of others with little or no effort to contribute to the mutual welfare, while others bend every effort to justify their existence. Some maintain themselves with reluctance, others with enthusiasm. Altered conditions may bring about a change in this regard in both organisms and pathologists and some who begin as pure parasites may adapt themselves to an independent status. Some refuse modification to meet changed conditions and survive or perish depending upon their own vigor and the severity of the environmental pressure.

Again, bacteria may be divided into the pathogens and non-pathogens. Occasionally, we see a situation that reminds us that this division may be made in us also. There are some individuals who always are making trouble for some one, usually their host. Existence apart from trouble-making is, for them, unthinkable. Others, fortunately enough, are never concerned in making trouble but carry on at peace with the world. As with bacteria, the non-pathogens are greatly in the majority and carry on a large number of activities that are vital for the normal life of the community. Some lowly organisms, for example, are able to fix atmospheric nitrogen; a thing which man accomplishes only by expenditure of vast sums of money and the building of elaborate machinery. These humble servants have kept us alive by their labors though they have been almost unknown, unhonored and unsung. Their efforts have been accepted without compensation and little thought of gratitude. They have been taken for granted and passed by. To draw an analogy would be painful.

Some bacteria are able to live on a very simple diet. Almost

any kind of food will do. They are not fastidious but tenacious of life under difficult conditions. Circumstances that would mean the death of the less hardy, mean nothing to them. Wherever they happen to fall, there they develop and only actual starvation, or summary destruction, stops them. And then there are those who do not, or think they do not, have their opportunity in one location and move about from place to place; never satisfied, never happy, always looking for something better and more nearly what they think they deserve. Everything has to be exactly right for them to maintain themselves long in any location. A great deal of pampering and petting, and most careful handling is necessary to keep them growing.

There are organisms whose chief claim to fame is that they are gas producers. The gas itself is usually of no value save as a means of identifying the organism. Sometimes it is the kind of gas, more often the amount, and frequently the circumstances leading to its formation that characterize the species. Further discussion on this point would be valueless.

Then there are the luminiferous bacteria. In some mysterious way they bring light out of darkness. They are not mere reflectors but makers of light and shine out "like a good deed in a naughty world."

And then, sad to relate, there are some whose life is accompanied by alcoholic fermentation.

If the analogy may be continued further it may be said that bacteria, which are quite definitely of pure strain ancestry, may be seen to develop in smooth or rough colonies, and the smoothness and roughness are more than superficial characteristics. Why pursue this throught further?

In recent years we have learned that bacteria may be completely destroyed by an ultra-microscopic substance, the bacteriophage, probably originated by the bacterium itself. The clinical pathologist finds himself similiarly attacked, and sometimes destroyed by the technician for whose beginning the pathologist himself was responsible.

Finally, it may be remembered that from the time of our first knowledge of bacteria until the present, there has been no change

in the salient characteristics of the bacteria known to us. May the same permanence of type be prophesied for clinical pathologists? For the family the answer is, probably, in the affirmative; for certain individual species, I think, there is no hope. The clinical pathologist who came into being because of a demand from his professional confréres for a peculiar kind of service and who established himself as an independent unit and continues to maintain himself without hospital or teaching connections is rapidly becoming extinct. Through competitive forces of various kinds he finds conditions more and more unfavorable and is maintaining himself at present only in comparatively few strategic locations.

This, to my mind, is a most interesting illustration of the evolution of a species, the radical change in the conditions affecting it, with the inevitable result following inexorable law. Much blame for the difficulty has been laid at the door of the technician whereas we forget that economic law operates in the practice of medicine as elsewhere. It is economically unsound for a high-priced worker to spend his time doing something that a low-waged worker can do as well. A manufactured article, to be sold, must be marketed at a reasonable price which must yield a reasonable profit to the producer. To keep the price within reasonable bounds and insure his profit the manufacturer cannot pay skilled men for unskilled labor. Labor costs must be commensurate with the labor done. Some of us, I fear, have forgotten that economic principles have their play in medicine as in business and have expected, through some more or less miraculous intervention, to have them set aside for our benefit. We should not be surprised when such intervention does not make its appearance. It is still true that "the laborer is worthy of his hire" but in these days when there is so much talk about the cost of medical care, uneconomic factors must inevitably succumb. The internist, or the surgeon, who finds himself confronted with the necessity of doing certain work for a fee which the patient may be able to pay and who requires assistance from the clinical pathologist and roentgenologist may find that after these are paid, what he has left is totally inadequate compensation for his own labor. To

meet this condition he resorts to some means by which he may secure what he terms routine examinations at a lower price and the clinical pathologist grumbles because of the loss of patronage. These conditions are not satisfactory to the clinical pathologist, or to the clinician. In due process of time evolutionary adjustment will bring about a greatly improved method of caring for this work. How much some of us may suffer, and how many of us shall be ground between the upper and the nether millstone depends upon whether we may be able to adapt ourselves to the rapidly changing conditions. That we, ourselves, may appreciably control the conditions seems to me a futile hope. After all, these are evolutionary processes moving in conformance to law. That some of us are hurt in the change is unfortunate but does not stop the movement.

It is probably not far from the truth that our specialty in medicine has come about as a result of evolutionary forces; that these forces are still operating; that changes in conditions necessitate changes in us; that some of us may survive while others perish. It is important, I believe, to recognize the fact that these various conditions are controlled by law, and that while we may be able to modify, or adjust, certain factors, to refuse to recognize these laws, to fail to admit their controlling influence, means a futile hope, impossible of realization.

On the other hand an intelligent adaptation offers the prospect of a greater usefulness and the greater security which we so much desire. The situation is not hopeless. A knowledge of the forces at work, a recognition of the laws by which they are governed, and a vision of the future based on this knowledge make it possible to adapt ourselves to the changing demands. An intelligent adaptation should see us through these days of transition and, though we may emerge vastly changed, we shall remain an integral and important factor in the science of medicine.

Program for the 1931 Convention at Philadelphia

The programs at the annual conventions are each year becoming longer and in order to prevent their becoming too long or too crowded it will be necessary to make some selection from the titles submitted.

Those who contemplate reading a paper at the coming convention are requested to send *as soon as possible* the title and an abstract of the paper to the Chairman of the Program Committee, Robert A. Kilduffe, M.D., Atlantic City Hospital, Atlantic City, New Jersey.

HEMATOLOGICAL ASPECTS OF AGRANULOCYTOSIS AND OTHER DISEASES ACCOMPANIED BY EXTREME LEUKOPENIA*

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The primary object of this communication is to present a classification based on the blood picture and histological changes in the bone marrow of the various diseases which are associated with a marked leukopenia.

The symptoms and blood picture are fairly diagnostic in certain conditions as in pernicious anemia, nutritional anemia or sprue, the various forms of splenomegaly (Gaucher's disease, splenic anemia and hemolytic icterus), and certain types of diseases of the lymphnodes after biopsy (Hodgkin's disease and lymphosarcoma). In Hodgkin's disease and sprue, septic manifestations and necrotic ulcerations of the mucous membranes are occasionally associated with the leukopenia.

Well-defined infectious diseases such as typhoid fever, and occasionally influenza, meningococcic sepsis, subacute endocarditis (with splenomegaly) and miliary tuberculosis may be accompanied by a marked diminution in the number of leukocytes. In a miscellaneous group (table 6) a certain number of cases of hepatitis (catarrhal jaundice), hyperthyroidism and a few cases of infectious mononucleosis (generalized transitory lymphadenopathy), especially in women, were noted to have a leukopenia; these patients often had fever and prostration, but no ulcerations of the mucous membranes were present. In a few women and one man there was persistent leukopenia of unexplained origin, or so-called idiopathic leukopenia.

* Read before the Ninth Annual Convention of the American Society of Clinical Pathologists, Detroit, Michigan, June 20–23, 1930.

The main groups which will be discussed pertain to the cases with a profound leukopenia (100 to 4,000 white blood cells), often showing septic manifestations, with necrotic lesions in the mucous membranes. Agranulocytosis is the most important member of this group. This, according to Schultz,[27] is a clinical entity of an apparently rapidly fatal septic condition with a characteristic leukopenia, associated with marked diminution or disappearance of the polymorphonuclear neutrophils or granulocytes. The differentiation of this disease from conditions simulating it is important. These are aplastic anemia (aleukia hemorrhagica), acute purpura hemorrhagica with a marked leukopenia and leukopenic leukemia. The underlying etiologic factors in this large group are not known. Certain toxic factors, however, may produce similar leukopenic and aplastic syndromes as in radium, x-ray, or benzol poisoning and following intravenous administration of salvarsan.

Diphtheria, septic sore throat, Vincent's angina and infectious mononucleosis may resemble agranulocytosis or agranulocytic angina[9] symptomatically but the blood pictures do not show the characteristic profound leukopenia in such cases. Vincent's spirilli may occasionally be present in the necrotic lesions of agranulocytosis. The marked septic manifestations of agranulocytosis are absent in the other various forms of ulcerative pharyngitis.[28]

I have had the opportunity of studying ninety cases of various diseases associated with marked leukopenia, exclusive of pernicious anemia and various forms of splenomegaly, malignant lymphadenopathies and cases treated with x-rays. According to the clinical manifestations and course, the following classification can be presented:

I. Fatal Agranulocytosis (table 1)
   A. Without anemia (Schultz), 4 cases
   B. With anemia (Brown), 6 cases
   C. Malignant leukopenia, 2 cases
II. Benign Agranulocytosis—Recovered cases, 14 cases (table 2)
III. Aplastic Myeloid Disorders (table 3)
   A. Acute aplastic anemia (aleukia hemorrhagica), 9 cases

B. Chronic aplastic anemia, 10 cases
C. Panmyelophthisis, 3 cases
D. Purpura hemorrhagica (with leukopenia), 1 case

IV. Leukopenic Leukemia, 15 cases (table 4)

V. Toxic Leukopenia or Aplastic Myeloid Disorders, as a Result of Poisoning with Benzol, Radium, and X-ray, Arsenic Arsphenamine, 6 cases (table 5)

VI. Miscellaneous Cases (Nutritional Anemia, Chlorotic Anemia, Endocrine Disorders, Hepatitis, Obscure Infections, Idiopathic Leukopenias), 20 cases (table 6)

FATAL AGRANULOCYTOSIS (TABLE 1)

A. Without anemia

These cases presented the typical syndrome first described by Schultz,[28] namely, fever, necrotic manifestations of the mucous membranes, prostration and occasionally jaundice. Türk reported a similar case in 1907, complicated by an endocarditis. In 127 cases, previously reported, women have been affected in 88 per cent. I have observed four additional cases, all in middle-aged women. The blood changes are typical and identical with those described by Schultz,[28] the white cells ranging from 200 to 4,000. There was almost complete disappearance of the polymorphonuclear neutrophils with relative increase in the percentage of lymphocytes. Occasionally a few plasma cells and macrophages were present. The bone marrow, examined in cases 1 and 2, showed the characteristic lesions such as complete disappearance of the myeloid cells. Only red cells, lymphocytes, plasma cells, megakaryocytes, and occasionally macrophages were seen.

B. With anemia

The first case of this type was reported in this country by Brown, as "a fatal case of acute primary infectious pharyngitis with extreme leukopenia." Schultz[29] did not accept such cases at first as agranulocytosis, but later modified his views. The anemia is usually moderate and may exist prior to the onset, or may result from the infection. In case 7, the patient suffered from menorrhagia, which caused the anemia. Thirty-four sim-

TABLE 1

FATAL AGRANULOCYTOSIS

CASE	SEX	AGE	LOCATION OF NECROSIS	BLOOD CULTURE	COURSE	HEMOGLOBIN	ERYTHROCYTES	LEUKOCYTES	PLATELETS	POLYMORPHONUCLEARS	LYMPHOCYTES	MONOCYTES	PLASMA CELLS	MACROPHAGES	BONE MARROW
						per cent				*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	
1	F.	33	Pharynx; anus; skin	*Strep.* [hemolytic] and *Esch. coli*	Relapsing	78	4,704,000	600	610,000		95	5			Typical
2	F.	48	Nasopharynx	*Staph. aureus*	Acute	84	4,350,000	400	240,000		99		1		Typical
3	F.	60	Pharynx	*Strep.* [hemolytic]	Acute	85	4,400,000	500	310,000		85	3	12		Not examined
4	F.	49	Pharynx; anus; skin	*Strep.* [hemolytic]	Relapsing	85	4,550,000	300	320,000	1	65	12	5	17	Not examined
5	F.	47	Tonsils; rectum; skin	*Ps. aeruginosa* and *Strep.* [hemolytic]	Acute	65	3,000,000	2,000	Normal		88	4	8		Typical
6	F.	50	Tonsils	Not done	Acute	70	3,840,000	1,700	210,000		89	11			Not examined
7	F.	54	Tonsil	Not done	Acute	62	3,000,000	400	260,000	2	89	6	3		Not examined
8	F.	28	Pharynx	*Strep.* [viridans]	Acute	74	4,100,000	1,200	250,000*		88		5	5	Typical
9	M.	56	Fauces; skin	Sterile	Acute	60	4,000,000	950	200,000*	14	83	3			Not examined
10	M.	62	None	Sterile	Acute	40	2,500,000	400	140,000	22	70	4	4		Not examined

* Followed by terminal thrombocytopenia.

ilar cases, twenty-nine in women and five in men have been reported. I have observed six additional cases (four women and two men). The hemoglobin varied from 60 to 74 per cent, red blood cells from 3,000,000 to 4,100,000, and white cells from 400 to 2,000. The blood platelets were normal in three cases but in cases 8 to 10 a terminal thrombocytopenia developed. The polymorphonuclear neutrophils varied from none to 14 per cent. The symptoms and course were similar to those in the group without anemia. The bone marrow in cases 5 and 8 was typical. In case 5 the bone marrow also showed numerous macrophages.

C. Malignant leukopenia

Cases 11 and 12 are interesting from the standpoint of the differential blood picture which showed a normal number of neutrophilic polynuclear cells, so that the diagnosis could not be agranulocytic but rather hypoleukocytic or malignant leukopenia. The symptoms, however, in case 11 were the same as in the agranulocytic type, fever, intense prostration and widespread ulceration of the pharynx and tongue. A few plasma cells and macrophages were occasionally present in addition to the premature polymorphonuclear cells.

In case 12 the symptoms, however, were those of an acute intense infection, such as high fever, up to 107°F., extreme prostration, and slight cough, but no ulcerations of the mucous membranes could be found. Some obscure lung signs were present in the chest indicating a bronchopneumonia, and the abdomen felt rather doughy. There was a secondary anemia and marked leukopenia (1,800 to 3,200 white blood cells). The x-ray examination of the chest later showed evidence of miliary tuberculosis.

The differential blood counts on cases 11 and 12 are in table 1a.

In such cases there is an overwhelming sepsis involving the bone marrow. This blood picture is certainly the one expected to result from such a primary infection. Such cases may prove to be of great importance in indicating the pathogenesis of agranulocytosis in which the infection is probably secondary and the changes in the bone marrow are possibly primary.

TABLE 1a

	CASE 11	CASE 12
Hemoglobin	74 per cent	60 per cent
Erythrocytes	3,800,000	3,200,000
Leukocytes	900	2,700
Platelets	430,000	180,000
Polymorphonuclears, young	12 per cent	2 per cent
Polymorphonuclears, staff	53 per cent	24 per cent
Polymorphonuclears, segmented	2 per cent	28 per cent
Lymphocytes	26 per cent	42 per cent
Monocytes	4 per cent	3 per cent
Myelocytes (neutrophilic)	2 per cent	None
Myeloblasts	1 per cent	None
Macrophages	None	1 per cent

AGRANULOCYTOSIS WITH RECOVERY (TABLE 2)

These are cases of agranulocytosis without a history of antisyphilitic treatment, or without other known cause. Twenty-seven patients (twenty women and seven men) have been reported as recovered following an attack of agranulocytosis. The variations in the leukocytes in these cases ranged from ninety-nine to 3,000. The largest number of recoveries, six cases, were reported by Friedemann. I have under observation at the present time fourteen cases which have recovered. Most of these cases had a profound leukopenia, varying from 800 to 1,500, and a few cases with a leukopenia varying from 3,000 to 4,600. All of the cases presented the agranulocytic syndrome of fever, more or less prostration and ulcerations of the mucous membrane. Case 24 showed no pharyngeal ulcerations, but signs of a bronchopneumonia were present. In most of the cases the blood picture did not correspond to the fatal type. In a few cases anemia was present; this was chlorotic in type (see table 6). The average leukocyte count was also higher as only one case had less than 1,000 leukocytes. The polynuclear cells varied from 5 to 35 per cent, and lymphocytes were relatively increased. Case 22 is

TABLE 2

AGRANULOCYTOSIS—RECOVERED CASES

CASE	SEX	AGE	LOCATION OF NECROSIS	BLOOD CULTURE	COURSE	HEMOGLOBIN	ERYTHROCYTES	LEUKOCYTES	PLATELETS	POLYMORPHONUCLEARS	LYMPHOCYTES	MONOCYTES	PLASMA CELLS	MACROPHAGES	BONE MARROW
						per cent				*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	
13	F.	21	Tonsils; gums	Sterile	Acute	80	4,500,000	1,600	190,000	16	79	3	1		Not examined
14	F.	48	Tonsils	Sterile	Acute	72	3,525,000	4,600	220,000	21	61	7	4	5	Not examined
15	F.	45	Tonsils; skin	Sterile	Acute	80	4,420,000	4,400	360,000	5	35	58	2		Not examined
16	M.	45	Gums	Not done	Acute	90	4,300,000	3,600	220,000	21	61	6			Not examined
17	F.	50	Tonsil	Not done	Acute	39	3,000,000	1,500	320,000	9	88	3	1		Not examined
18	F.	32	Tonsil	Not done	Acute	95	5,100,000	5,100*	350,000	35	58	3			Not examined
19	F.	38	Tonsils	Not done	Acute	90	4,400,000	3,000	240,000	30	60	4			Not examined
20	F.	56	Tonsils	Not done	Acute	85	4,600,000	1,800	180,000	18	56	15			Not examined
21	F.	49	Tonsil; rectum	Not done	Acute	60	3,500,000	800–1,800	370,000	48	42	10			Not examined
22	F.	45	Tonsils; sinusitis	Sterile	Chronic	32	4,100,000	3,100	260,000	88†	10	2			Myeloid hyperplasia
23	M.	45	Tongue	Sterile	Chronic	52	3,136,000	1,400	210,000	12	50	16‡			Not examined
24	F.	50	None; bronchopneumonia	Sterile	Acute	60	3,450,000	2,240	200,000	29	54	17			Normal; light hyperplasia
25	F.	17	Tonsil	Not done	Acute	85	4,800,000	4,500	250,000	24	72	4			Not examined
26	F.	36	Tonsils	Not done	Acute	80	4,500,000	2,400	320,000	22	60	16	2		Not examined

* Two weeks after the attack.

† Aleukocytosis polynucleosis.

‡ Seventeen per cent myelocytes and myeloblasts. Leukopenia persists five years later.

of the leukopenic type, with 88 per cent polymorphonuclear cells. A certain number of the cases in this group are still being followed and cases 22 and 23 after five years without symptoms still show a leukopenia as low as 1,500. In following up such cases I am led to believe that there is an associated constitutional factor which is either transitory or permanent in the production of the leukopenia and which may account for the peculiar reaction to the infection.

Case 22, an unusual case of unexplained edema, shows some evidence of endocrine disturbance such as myxedema, and sparcity of hairs, and a lowering of the basal metabolism. Biopsy of the sternum was done in this case and the bone marrow was found to be hyperplastic. At the time the bone marrow was removed, there was a marked leukopenia—2,000 white blood cells in the peripheral blood.

In case 23 nephrectomy was performed for calculus pyonephrosis. The blood was examined after the operation on account of sluggish progress of the wound and hemorrhage. The patient complained of a sore tongue on which a few ulcerations were present. The blood picture showed a marked leukopenia, a few myelocytes and myeloblasts and marked diminution of the polymorphonuclear cells. Following a blood transfusion, the patient made an uneventful recovery. The myelocytes and myeloblasts were not found on subsequent examinations, but for the past five years the blood examinations showed a constant leukopenia, neutropenia and relative lymphocytosis. Otherwise the blood picture was normal. The general condition is good and the patient is symptomatically well.

This large group of recovered cases, rather heterogeneous in character, corresponded to the fatal group of cases of agranulocytosis as far as the early symptoms were concerned. There is no doubt, however, that in the fatal cases the underlying pathological lesions in the bone marrow were relatively different. Here there was a complete absence of myeloid elements. In cases twenty-two and twenty-four which recovered the bone marrow showed evidence of hyperplasia. The septic manifestations in this latter group were most likely primary, with some inhibitive or toxic re-

action on the bone marrow. In some cases there was an underlying constitutional disturbance[3], resulting in diminution of the leukocytes, prior to the onset of infection, while in others the leukopenia was the result of the infection. In the fatal agranulocytic group there seemed to be a widespread disease of the bone marrow, of an aplastic nature, limited to the myeloblastic and myelocytic portion of the bone marrow, so that there was a lack of resistance against even slight infections on account of the absence of the polymorphonuclear cells in the peripheral blood. In a few cases there may be temporary improvement or remission, but the patient usually succumbs during the second or third relapse.[20] According to the blood picture and the granulopoietic aplasia in the bone marrow, fatal agranulocytosis appears to be a clinical entity.

APLASTIC MYELOID DISORDERS (TABLE 3)

Acute aplastic anemia, described by Ehrlich, usually runs a rapid course. Severe anemia is present from the onset and is out of proportion to the hemorrhages as the result of the associated hemorrhagic condition. The blood picture is typical and shows a constant and progressive reduction in the number of red cells. The white cells and blood platelets are also greatly diminished. The coagulation time is usually normal, and the bleeding time is increased. The tourniquet test is positive and the clot retraction is absent or diminished. These reactions are similar to those of purpura hemorrhagica. The course of aplastic anemia varies from one week to three months and may be prolonged by blood transfusions. In the chronic form of this disease the course may run as long as five years. The hemorrhagic manifestations are not so severe as in the acute type. The mode of exitus in cases of aplastic anemia is usually exsanguination or cerebral hemorrhage.

In a few cases secondary infections may occur with necrotizing lesions of the mucous membranes and skin, and clinically the condition may simulate agranulocytosis. This particular septic course may be present from the onset. The clinical syndrome showing severe anemia, hemorrhagic manifestations and necrotizing lesions in the mucous membranes has been called "aleukia

TABLE 3

CASE	AGE	SEX	LOCATION OF NECROSIS	HEMOGLOBIN	ERYTHROCYTES	LEUKOCYTES	PLATELETS	POLYMORPHONUCLEARS	LYMPHOCYTES	MONOCYTES	OUTCOME
Acute aplastic anemia											
				per cent				*per cent*	*per cent*	*per cent*	
27	22	F.	Intestines	29	1,500,000	800	20,000	25	60	5	Dead
28	24	M.	Subcutaneous	31	1,600,000	800	5,000	14	85		Dead
29	24	M.	None	28	1,300,000	900	10,000	8	82	8	Dead
30	17	M.	Pharynx	22	1,330,000	800	2,000	12	86	2	Dead
31	20	F.	Pharynx	15	828,000	1,200	1,500	19	67	5	Dead
32	21	F.	None	22	1,800,000	8,800	10,000	14	81	5	Dead
33	20	M.	Pharynx	27	1,100,000	1,000	80,000	22	72	1	Dead
34	50	M.	Pharynx	35	1,820,000	1,200	10,000	16	82	2	Dead
35	10	F.	Pharynx	18	690,000	750	4,000	1	96		Dead
Chronic aplastic anemia											
36	6	M.	None	25	1,600,000	1,200	4,000	3	94		Dead
37	7	M.	None	68	3,500,000	2,400	2,200	22	69	8	Dead
38	6	M.	None	44	2,048,000	2,100	30,000	3	97		Dead
39	7	F.	None	28	1,600,000	4,000					Dead
40	3	F.	Pharynx	45	2,800,000	2,400	70,000	27	65	10	Dead
41	10	M.	None	69	3,900,000	3,800	20,000	22	72	5	Dead
42	16	F.	Pharynx	30	1,460,000	1,900	40,000	22	75	3	Dead
43	9	F.	None	26	1,600,000	2,900	25,000	35	60	4	Dead
44	62	F.	Pharynx	62	3,200,000	600*	40,000	14	66		
45	25	F.	None	35	1,500,000	3,000	60,000	40	51	8	Dead
Chronic myelophthisis											
46	4	F.	Pharynx; skin; periostium	32	2,240,000	3,800	290,000	26	73	1	Dead
47	17	F.	Broncho-pneumonia	18	1,190,000	3,800	310,000	24	68	7	Dead
48	8	M.	None	32	1,700,000	3,200	130,000	38	58	2	Unimproved

* Sixteen per cent plasma cells.

hemorrhagica," by Frank. Later investigations may show that this septic type may possibly be a distinct clinical entity, closely

related to aplastic anemia. Aleukia hemorrhagica may resemble purpura hemorrhagica associated with a leukopenia and without splenomegaly. In purpura hemorrhagica, however, an anemia is not present at first but develops as the hemorrhages increase. The blood examinations in such a case in a male aged eighteen years, are given in table 3a.

TABLE 3a

	FEBRUARY 13, 1930	FEBRUARY 18, 1930	FEBRUARY 19, 1930
Hemoglobin	105 per cent	73 per cent	62 per cent
Erythrocytes	6,000,000	4,000,000	3,900,000
Leukocytes	2,600	2,800	2,800
Platelets	20,000	20,000	50,000
Polymorphonuclears, staff	20 per cent	24 per cent	5 per cent
Polymorphonuclears, segmented	46 per cent	36 per cent	48 per cent
Polymorphonuclears, eosophilic	1 per cent	None	4 per cent
Lymphocytes	32 per cent	35 per cent	36 per cent
Monocytes	11 per cent	5 per cent	7 per cent
Coagulation time	12 minutes	9 minutes	
Bleeding time	4 minutes	92 minutes	
Tourniquet test	Positive	Positive	
Clot retraction	None	None	

The examination of the bone marrow in this particular case also showed a very marked diminution of the granulocytes. Similar cases of this type which I have observed, did not show any evidence of a septic invasion.

Some cases of thrombocytopenic purpura hemorrhagica with leukopenia may be accompanied by a splenomegaly. These cases are more benign and usually recover following splenectomy.[24]

There is still another type of an aplasia of the bone marrow which is known as "panmyelophthisis." I believe that this term should be restricted to cases which are characterized by a severe anemia and leukopenia, but in which there is no hemorrhagic tendency. The blood platelets are normal at first but may diminish late in the disease. In a few such cases sepsis with or

without necrotic ulcerations may occur. These cases are usually chronic and afebrile however.

Twenty-one cases of the various forms of aplastic anemia have been observed in the past fifteen years. At the onset the blood examinations always showed a severe anemia varying from 10 to 50 per cent. The leukocyte count in most of the cases was below 3,000 although rarely a transitory rise took place. There was a relative lymphocytosis, but the polynuclear cells varied from 5 to 40 per cent. In late stages of the disease, with an associated infection, the polynuclear cells sometimes showed a profound depression. In all of the cases of acute and chronic aplastic anemia there was a thrombocytopenia (blood platelets varying from 2,000 to 20,000), and as a rule this was associated with a marked hemorrhagic diathesis. The differential count showed an occasional myelocyte or myeloblast, rarely over 5 per cent; reticulocytes were absent or reduced.

The bone marrow was examined in these three groups and was apparently the same in all cases. Usually there is a hypoplasia of the red cells. The megakaryocytes were very greatly diminished and sometimes were absent. The leukocytic elements usually consisted of a moderate number of lymphocytes, myelocytes and myeloblasts. In the myelophthisic group there was considerable lymphocytic infiltration and usually more megakaryocytes were seen. A diminution of the mature myeloid cells was evident in all types of aplastic anemia.

LEUKOPENIC LEUKEMIA (TABLE 4)

This group very frequently causes confusion between aplastic anemia and other cases associated with secondary infections, especially of the tonsils, followed by necrotic manifestations simulating agranulocytosis. The blood picture in this group varies with respect to the red blood cells and the blood platelets which are usually diminished. The white blood cells may be very greatly reduced in number and associated with a constant increase of abnormal myeloid cells. Leukopenic leukemia may not necessarily be the same disease entity as myeloid leukemia of the leukocytic type, but may be the result of sclerotic or fatty

changes in the hematopoietic organs with myeloid metaplasia of the liver, spleen and lymph-nodes, with the presence of premature myeloid cells in the circulating blood. In other cases the typical lesions of leukemia are found in the bone marrow.

TABLE 4

LEUKOPENIC LEUKEMIA

CASE	AGE	SEX	LOCATION OF NECROSIS	HEMOGLOBIN	ERYTHROCYTES	LEUKOCYTES	PLATELETS	POLYMORPHONUCLEARS	LYMPHOCYTES	MONOCYTES	MACROPHAGES	MYELOBLASTS	OUTCOME
				per cent				*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	
49	12	M.	Pharynx	39	1,920,000	2,200	205,000	17	51	2		27	Dead
50	7	M.	Pharynx	40	2,300,000	4,800	260,000	5	55	4	6	29	Dead
51	34	M.	None	56	3,800,000	3,700	60,000	1	12	1		69	Dead
52	42	F.	Pharynx	50	2,600,000	2,000	6,000	6	52	2	5	35	Dead
53	46	F.	None	23	1,400,000	2,500	140,000	61	26	3	4.4	3.6	Dead
54	56	F.	None	30	1,400,000	4,000	20,000	41	39	8	4	5	Dead
55	45	M.	None	33	1,600,000	2,000	20,000	34	48	3	8	8	Dead
56	7	M.	None	29	1,800,000	1,500	10,000	6	60		1	31	Dead
57	53	F.	Pharynx	62	3,240,000	4,000	20,000	5	37		3	51	Dead
58	63	M.	None	56	3,200,000	3,100	220,000	13	36			49	Dead
59	50	F.	None	32	1,700,000	2,000	50,000	12	56			32	Dead
60	44	F.	None	65	3,500,000	2,500	80,000	24	40	2	2	28	Dead
61	6	M.	None	30	1,000,000	750	5,000	30	20	2		48	Dead
62		F.	None	40	2,800,000	2,200	100,000	4	64	2	6	6	Unimproved
63		F.	None	16	800,000	4,000	70,000	33	27	2	18	18	Unimproved

The differential count in these cases is of great importance and should be studied very carefully with the Jenner-Giemsa stain; myeloblastic cells may also be detected by means of the oxidase reaction. In certain cases of profound leukopenia the method of Mengler may be used in concentrating the white blood cells, by

centrifuging citrated blood and using the top layer of the red blood cells for making the blood smears. In this manner a larger number of leukocytes are presented in the blood smears in cases of marked leukopenia. Occasionally myeloblasts have been found in agranulocytosis, as in the case of von Domarus. Case 23 showed a moderate number of myeloblasts on the first examination. The patient recovered but for the past five years has shown a constant leukopenia (less than 2,000) and relative lymphocytosis, but no premature myeloid cells. However, the constant appearance of myelocytes and myeloblasts in the peripheral blood is a characteristic diagnostic observation. The leukocytes may greatly diminish suddenly and fall to as low as 750 (case 61). Herz reported a typical leukopenic leukemia with 800 leukocytes, mainly myeloblasts in type. Frank made note of a similar case, which was followed by apparent recovery and later developed a leukocytic myeloblastic leukemia. A few cases reported as agranulocytosis are undoubtedly leukopenic leukemia with or without secondary necrotic septic manifestations. Table 4 shows the reports of the blood pictures in fifteen cases of leukopenic myeloid leukemia. Leukopenic lymphoblastic leukemia is very rare, especially cases with less than 5,000 leukocytes.

TOXIC LEUKOPENIAS AS A RESULT OF POISONING WITH BENZOL, RADIUM AND X-RAY, ARSENIC AND ARSPHENAMINE

About forty cases with profound leukopenia associated with or following anti-syphilitic treatment with neosalvarsan have been reported. The symptoms in some cases resemble those of agranulocytosis and in others those of aplastic anemia. Aubertin and Lévy have suggested the following classification of the agranulocytic types:

1. Agranulocytic form
2. Associated forms
   - A. Agranulocytosis, moderate anemia and hemorrhagic diathesis
   - B. Agranulocytosis, severe anemia and hemorrhagic diathesis
3. Formes frustes—same as above but only slight changes of the polymorphonuclear cells

Five additional cases have been observed. Case 64 apparently resulted in a chronic aplastic anemia. So far no ulcerations of the mucous membranes have appeared.

Cases 65, 66, and 67 belong to the agranulocytic group. Case 66 made a complete recovery. The bone marrow from the sternum was examined during the leukopenic period of this patient and was found to be hypoplastic. The bone marrow in case 67 showed the typical findings of agranulocytosis, with a complete disappearance of myeloid cells and apparent replacement by lymphocytes and plasma cells.

TABLE 5

AGRANULOCYTOSIS FOLLOWING SALVARSAN THERAPY (CASES 64 TO 68) AND BENZOL POISONING (CASE 69)

CASE	AGE	SEX	LOCATION OF NECROSIS	HEMOGLOBIN	ERYTHROCYTES	LEUKOCYTES	PLATELETS	POLYMORPHONUCLEARS	LYMPHOCYTES	MONOCYTES	PLASMA CELLS	OUTCOME
				per cent				*per cent*	*per cent*	*per cent*	*per cent*	
64	36	M.	None	45	3,200,000	2,400	30,000	37	60	3		Improved
65	38	F.	Pharynx	42	2,250,000	500	50,000		94	4	2	Dead
66	35	F.	Pharynx	67	3,650,000	3,200	150,000	5	31	54		Well
67	53	M.	Pharynx	78	3,800,000	1,000	60,000		86		14	Dead
68	35	F.	Pharynx	73		2,300		45	41	14		Dead
69	45	M.	None	27	1,800,000	1,700	30,000	34	52	7		Improved

In all cases there was a secondary anemia, more or less severe, a leukopenia (white blood cells 2400) and a marked thrombocytopenia (30,000 to 60,000 platelets). There was marked diminution of the polymorphonuclear neutrophils and a relative leukocytosis. In case 67, 14 per cent plasma cells were present.

One case of benzol poisoning is at present under observation. The blood picture corresponds to that of aplastic anemia. The condition is gradually improving after transfusions. The red cells and blood platelets have increased, but the leukocytes are still less than 2000 in number.

The leukopenia following x-ray and radium treatment for non-leukemic conditions is sometimes followed by a profound leukopenia which subsides after the treatment has been stopped. A few cases of x-ray poisoning have been reported in which the findings are those of chronic aplastic anemia (Wegelin).

In Hodgkin's disease, the x-ray treatment may produce a marked leukopenia, sometimes associated with a marked reduction in leukocytes. There are also cases of Hodgkin's disease which may have a constant leukopenia, as a result of bone marrow involvement, or as a result of aplasia of the bone marrow from x-ray treatment. The leukocytes in some cases may fall as low as 240 and the symptoms before exitus may resemble those of agranulocytosis (Miller).

Martland has called attention to the anemia and leukopenia occurring in radium workers which he calls leukopenic anemia of the regenerative type. I have made examinations of three cases of radium poisoning and can confirm the blood picture of aplastic anemia as described by Martland. In one case the blood picture was similar to that of aplastic anemia. In two others there was a severe anemia and leukopenia, but the blood platelets were not greatly diminished as in cases of panmyelophthisis and the relative percentage of the lymphocytes was undisturbed. In these two cases the typical osteonecrosis of the mandible was present. The staff polynuclear cells were increased in these two patients. In one case, basophilic-like granules (toxic) were present in the staff polynuclear cells.

MISCELLANEOUS CASES (NUTRITIONAL ANEMIA, CHLOROTIC ANEMIA, ENDOCRINE DISORDERS, HEPATITIS, OBSCURE INFECTIONS, IDIOPATHIC LEUKOPENIAS)

This series of cases indicates the relative frequency of leukopenia in certain conditions without the necrotic lesions in the mucous membrane. The leukocytes in this particular group varied from 3,000 to 6,000. Most of the cases had a relative lymphocytosis. Six of these cases ran a typical course of infectious mononucleosis, fever, generalized lymphadenopathy, and splenic enlargement. A few cases of this type may develop

necrotic lesions in the mucous membranes and may resemble agranulocytosis. Such patients recover. Case 15 was of this type and showed an unusual increased number of monocytes resembling the monocytic angina of Schultz.[30] The cases of von Domarus and Kohn, as a result of salvarsan, were similar in character. Some cases of chlorotic anemia and liver disease also showed a leukopenia. A few cases of typical influenza were also associated with a leukopenia. In a few cases the cause of the leukopenia could not be determined, and were considered constitutional in character.

In one case of cirrhosis of the liver, with a white cell count of 4,000 and 74 per cent polynuclear cells, the patient later developed a gangrenous appendicitis. The leukocyte count during this attack rose to 8,000 with about 78 per cent polynuclear cells, of which 12 per cent were staff forms. In similar cases where a leukopenia precedes the infection, a leukocytosis may be considered to range from 7,000 to 10,000, in contradistinction to the leukocytosis of 14,000 to 20,000 white cells in the normal individual.

The leukopenia in these various miscellaneous cases indicates the difference in the reaction of certain individuals, especially women, and that leukopenia is much more prevalent than is generally suspected.

ADRENALIN REACTION IN CASES OF AGRANULOCYTOSIS

The reaction of adrenalin in normal individuals is well known. From fifteen to forty-five minutes after the injection of 1.0 mgm. of adrenalin subcutaneously, one usually observes a leukocytosis of a varying degree. Licht and Hartmann observed no leukocytosis in their case of agranulocytosis following the injection of adrenalin. Benhamou found a definite increase of the leukocytes in a fatal case, and Stockinger found a definite leukocytosis in a benign case of agranulocytosis following the injection of adrenalin. In leukopenic leukemia and aplastic anemia a marked rise of the leukocytes is found after adrenalin injection. Adrenalin produced only a slight increase in the leukocytes from 2,000 to 3,000 in case 4 a fatal case of agranulocytosis. The rhythm of the white

cells was also studied in this same case, but there was only a very slight inconstant change every fifteen minutes in the number of the leukocytes. The adrenalin reaction may prove to be an important indication of the potency of the bone marrow and other tissues and differentiate the genuine cases of agranulocytosis from allied conditions.

THEORETICAL CONSIDERATIONS OF LEUKOPENIA

Leukopenia may be considered the result of intrinsic or extrinsic influences on the hematopoietic organs which are the source of the leukocytes, namely: the bone marrow; lymph-nodes, and possibly other areas, such as the reticulo-endothelial tissue which may have leukopoietic potentialities. The extrinsic factors in the regulation of the white blood cells are the vegetative nervous system, infection, and the acid-base equilibrium of the body.

According to the recent observations of Mueller and Hoff, there is some proof that the vegetative nervous system influences the circulating leukocytes. The action of various drugs such as adrenalin, atropin and pilocarpin, ingestion of milk, as in the Widal, hemoclastic crisis, are well known examples of reactions on the vegetative nervous system. Mueller has shown that the intradermal injection of foreign protein, such as aolan, produces a peripheral leukopenia. He has also pointed out that the red blood cells are not involved in this mechanism. His experiments also indicate that there is a splanchno-peripheral correlation, so that when the leukopenia occurs in the peripheral blood vessels, there is a marked increase of the white blood cells in the splanchnic area. The injection of adrenalin produces a reversal of the leukocytic distribution (Mueller and Hoelscher[22, 23]).

Infection is another important influence on the leukopoietic organs. This is possibly the most outstanding factor in the study of leukopenia. The ordinary infections produce a marked polynucleosis, especially in the early stages, such as the staff polynuclear cells, which, according to Schilling[25] are accompanied by marked regenerative changes in the bone marrow. According to this observer, there are three phases in the reaction of the hematopoietic organs to infection: (1) The polynuclear

TABLE 6

MISCELLANEOUS CASES ASSOCIATED WITH LEUKOPENIAS

CASE	DIAGNOSIS	AGE	SEX	HEMOGLOBIN	ERYTHROCYTES	LEUKOCYTES	PLATELETS	POLYMORPHONUCLEARS	LYMPHOCYTES	MONOCYTES	PLASMA CELLS	OUTCOME
				per cent				*per cent*	*per cent*	*per cent*	*per cent*	
70	Infectious mononucleosis	28	F.	70	4,650,000	4,700	220,000	34	53	7	5	Well
71	Infectious mononucleosis	8	F.	82	5,050,000	4,500	180,000	30	65	3		Well
72	Infectious mononucleosis	36	M.	85	4,500,000	4,300	320,000	50	43	4		Well
73	Infectious mononucleosis	22	M.	100	5,400,000	4,600	260,000	36	55	8		Well
74	Infectious mononucleosis	26	F.	68	3,840,000	4,800	320,000	26	68		2	Well
75	Tibial periostitis; arteriosclerosis	70	M.	85	4,800,000	3,500		10	86	3		Unimproved
76	Hepatitis	40	M.	78	4,000,000	3,700	200,000	55	36	4		Well
77	Hepatitis; jaundice	35	F.	84	5,100,000	4,200	200,000	27	44	42	3	Well
78	Neurosis	42	F.	82	4,900,000	3,800	350,000	50	47	3		Unchanged
79	Infectious mononucleosis	32	F.	92	4,900,000	3,200	320,000	59	34	6		Well
80	Carcinoma and Hodgkin's disease	56	M.	47	2,500,000	900*	110,000	61	24	12		Dead
81	Hepatitis	29	M.			4,200		44	49	6		Well
82	Cirrhosis of liver	65	F.	42	2,500,000	3,200	310,000	75	18	5		Dead
83	Cirrhosis of liver	50	M.	100	5,340,000	4,000	190,000	74	20	6		Well
84	Ecchymoses	38	F.	76	4,950,000	4,000	240,000	57	39	3		Improved
85	Menorrhagia		F.	70	3,800,000	2,300	140,000	36	41	12		Well
86	Chlorotic anemia	22	F.	56	5,000,000	4,200	420,000	39	50	11		Well
87	Nutritional anemia	45	M.	36	2,000,000	3,800	50,000	62	25	12		Well
88	Hyperthyroidism	40	F.	65	3,800,000	3,000	260,000	40	55	5		Improved
89	Influenza	40	F.	87	5,800,000	4,200	450,000	61	38	1		Well

* Received x-ray treatment.

increase; (2) monocytic increase; and, (3) increase of lymphocytes and eosinophils during the post-infectious stage.

Other types of atypical infections are accompanied by an increase of the lymphocytes or monocytes (infectious mononucleosis). The relation of certain types of organism associated with such lymphocytosis has been suggested. Witts and Welb found a monocytosis following injections of the Bacterium monocytoides in rabbits. Not infrequently infectious mononucleosis may be preceded by a moderate leukopenia and may not show a leukocytosis at any stage of the disease (cases 70–74, 79, table 6).

Certain forms of long-continued streptococcus viridans bacteremias may be associated with an increase of the reticuloendothelial cells or macrophages in the ear blood (Schilling[26] and others). Such cases may show a marked leukopenia in the finger blood and leukocytosis in the ear blood. However, sub-acute bacterial endocarditis with splenomegaly, may be accompanied by marked leukopenia. Certain types of fulminating sepsis (meningococcus, staphylococcus, typhoid fever, miliary tuberculosis (case 12)) involve the bone marrow to a very great extent, and may be associated with a marked leukopenia. Other types of sepsis of long duration, bacteriemia and even overwhelming fulminating bacteriemia are accompanied by leukocytosis. In such instances the young and staff polynuclears are increased from 20 to 60 per cent. Large numbers of these young polynuclear cells show basophilic granulation. These granules have been called toxic granules by Gloor and Barta believes that these granules are possibly ingested particles. These cells also indicate a poor prognosis. Vacuolization of the polynuclear cells with toxic granules is also sometimes present in these severe infections. In the agranulocytic conditions the few polynuclear cells occasionally found may show the toxic granules.

Hormones and the acid-base equilibrium of the blood[13] may also be factors in the regulation of the number of circulating leukocytes. It is well known that certain products broken down in the stomach by the action of the gastric juice, may have a profound influence on the red blood cells[6] but, as yet, sufficient proof has

not been brought forward concerning the action of similar substances on the leukopoietic tissue. In the miscellaneous group, cases of hyperthyroidism and hypothyroidism are noted, with marked leukopenia. One of the cases of agranulocytosis which recovered also showed evidence of hypothyroidism associated with severe chlorotic anemia. Friedemann pointed out a possible relationship of endocrine disturbances with leukopenia in one of his reports on agranulocytosis.

The constitutional factor may be of very great importance, and may explain the increased frequency of agranulocytosis in females. It is not infrequent for some of the patients who develop agranulocytosis to have a constant leukopenia or a tendency to a leukopenia as a result of some primary disturbance of the granulopoietic tissues. These tissues may be somewhat diminished, compared to the normal, or may be sluggish in the production of polynuclear cells in the presence of an infection. The bone marrow may become rapidly exhausted from even a slight infection, so that the defense mechanism against infections may be reduced to a minimum, resulting in the characteristic lesions which are found in agranulocytosis, namely: the necrosis without an inflammatory reaction. This occurs in areas, where numerous organisms are usually present, such as the respiratory and gastro-intestinal tracts. Kleeberg showed that in animals rendered agranulocytic, the anti-bacterial power in the blood is considerably diminished.

Leukopenia may be either of a transitory nature or permanent. In one of my recovered cases of agranulocytosis, the leukocyte count has never been above 2,000 for the past five years. In other cases, leukopenia has been found prior to the onset of the disease. The study of the underlying cause of the constitutional factor is likely to help in solving the problem. The leukopenia in itself, which may be found in certain women who have never had real attacks of agranulocytosis, may not be associated with any symptoms, which appear when the secondary infection takes place. In the eighty-nine cases reported in this paper, 64 per cent were in females. In the agranulocytic groups there is a marked preponderance, 85 per cent of females affected.

DISCUSSION OF BLOOD PICTURES IN LEUKOPENIC STATES

In the various groups outlined, the blood picture may be considered of diagnostic and prognostic importance. In the fatal cases of agranulocytosis, the main characteristic is a profound leukopenia of less than 1,000 white blood cells and the complete disappearance of the polynuclear leukocytes (granulocytes), whereas the blood platelets are normal except for a terminal thrombocytopenia. In the rare form of malignant leukopenia, the symptoms may be identical, but the profound leukopenia is accompanied by a corresponding diminution of the three types of leukocytes. The polynuclear cells in this condition are mainly of the staff variety with toxic granules. A moderately severe anemia may be present.

The recovered cases of agranulocytosis exceptionally show such a profound leukopenia, and are rarely accompanied by complete disappearance of the polynuclear cells. As in the fatal cases, the red cells are usually normal or slightly subnormal and there is an absence of a hemorrhagic tendency.

In the aplastic disorders of the bone marrow which involve more than one system, there are three well-defined groups, although some variations occur within each group. In aplastic anemia, either acute or chronic, a marked diminution of all the cellular elements of the blood are found, mainly anemia, leukopenia, and thrombocytopenia, and the differential count shows a relative lymphocytosis. In addition to the hemorrhagic diatheses, septic manifestations may occur (aleukia hemorrhagica), with a profound terminal leukopenia and disappearance of the polynuclear cells. In panmyelophthisis there is a deficiency of the hematopoietic and leukopoietic elements, without involving the blood platelets. Terminal sepsis simulating agranulocytosis can also occur in this aplastic type of blood disease. An atypical type of purpura hemorrhagica with marked leukopenia, but without splenomegaly may occur. In this condition the leukocytes and blood platelets alone are involved, and anemia results from loss of blood.

All these aplastic bone marrow changes, including agranulocytosis, may result from poisoning with benzol, radium and x-ray, arsenic, and arsphenamine.

Leukopenic leukemia is sometimes accompanied by a profound leukopenia, but the differential blood count is characterized by the presence of premature myeloid cells, such as myeloblasts and myelocytes and rarely lymphoblasts. Secondary septic manifestations may occur and occasionally simulate agranulocytosis.

There is sufficient evidence to indicate that the histological examination of the bone marrow also shows characteristic lesions in these various groups. These usually correspond to the blood changes, but in some cases there is marked discord between the leukopenia and the hyperplastic histological picture of the bone marrow especially in the benign cases of agranulocytosis. In this latter group, the cause of the leukopenia must be considered extrinsic in character. In the main groups, however, such as fatal agranulocytosis, the aplastic anemias and leukopenic leukemias, the bone marrow changes correspond with the blood picture. This points to a primary disease of the bone marrow. Septic manifestations result from the deficient formation of the granulocytes and hemorrhagic disorders are due to blood platelet deficiency.

SUMMARY

1. Ninety cases of marked leukopenia that resulted from various disturbances are presented.

2. The main cause of the leukopenia is believed to be primary in aplastic constitutional disturbances of the bone marrow:

A. Fatal agranulocytosis as the result of some profound disturbance in the formation of the granulocytic element.

B. Aplastic anemia as the result of widespread aplasia of all the elements in the bone marrow.

C. Panmyelophthisis resulting in diminution of the red and white blood cells.

D. Purpura hemorrhagica with leukopenia where the white blood cells and blood platelets are involved.

3. Leukopenic myeloid leukemia may symptomically resemble some of these blood conditions, but the constant presence of the characteristic myeloblasts and myelocytes or lymphoblasts in the peripheral blood is important for the differentiation of this particular disease.

4. A benign form of agranulocytosis also occurs as a result of infection. The bone marrow in such cases is not aplastic.

5. Direct toxic action on the bone marrow caused by benzol, radium, x-rays, salvarsan, may produce various blood pictures of agranulocytosis and other aplastic conditions (aplastic anemia, myelophthisis, and purpura hemorrhagica).

6. A large number of miscellaneous cases are also noted. These show a more or less severe leukopenia (infections, liver disease, obscure leukopenias, Hodgkin's disease, chlorotic anemia, pernicious anemia, and carcinoma with metastases to the bone marrow, and various forms of splenomegaly).

7. The study of the blood picture establishes certain criteria for the differentiation of the various diseases associated with marked leukopenia.

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AGRANULOCYTIC SYNDROMES*

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Ever since the classical studies of Arneth, Tuerk, von Jagic and others, the pathological reactions of the leukopoetic system have been observed and followed with intense interest by a large number of clinical hematologists who contributed valuable data to the clinical branch of hemopathology.

The great variety in the leukocytic picture found under various circumstances as well as under apparently identical situations led to discrepancies of opinions and to divergences in interpretation of the observations on the peripheral blood. We need only to point out the interesting question of the malignant myeloblastic reaction of the blood, of the monocytic blood picture, of the rapid disappearance of granulocytes from the blood stream, and so forth, all hematological reactions, complexes and syndromes not uncommonly observed in connection with systemic infections and toxemias, often caused by one and the same bacterial group.

In 1922, W. Schultz tried to separate a peculiar nosological entity under the name of agranulocytosis. These cases were characterized by sudden onset with high fever and malaise, development of ulcerous-necrotic, diphtheritic-gangrenous processes in the mouth, particularly localized on the tonsils, pharynx, gingiva, and soft palate, or in mucous surfaces of some other organs, such as the esophagus, colon, and vagina, and absence of icterus and hemorrhagic diathesis. Enlargement of the spleen and liver was only occasionally observed whereas lymph nodes did not show any swelling. The blood changes were characterized by a rapid drop in the number of white blood cells (leukopenia) with a nearly complete disappearance of granulocytes (neutro-

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philes and eosinophiles). The erythrocytic blood picture did not exhibit any alterations and the platelets were also unaffected. A lethal outcome followed rapidly. In two of the first five cases Schultz cultured pneumococci from the blood stream. Schultz was emphatic in postulating for this sharply outlined symptom complex the term agranulocytosis, which he desired to introduce as a definite disease.

Schultz' agranulocytosis is not the result of a specific etiological factor (*Diplococcus pneumoniae*, Streptococcus [hemolytic], *Escherichia coli*, *Pseudomonas aeruginosa* were found), but is, as the author claims, a characteristic symptom complex deserving to be accepted as a definite nosological entity.

Since 1922, many observations have been made and papers have been published in rapid succession, partly confirming, partly modifying and supplementing the original statements of Schultz. Some authors included in their discussion particularly the damages to and reactions of the erythropoetic system, cases which according to our experience show a complete functional exhaustion of the entire bone marrow.

SUMMARY OF CASES

Since 1925, we have observed twenty-two cases of abnormal reactions of the leukopoetic system in individuals showing ulcerous-gangrenous processes of the oral cavity. This present study, which is presented as a preliminary report, is based upon seventeen cases, involving twelve males, ranging in age between five and fifty-two years, and five female patients, whose ages varied between twenty and eighty-three years. All but two of the patients died.

Our cases can be summarized as follows: so-called agranulocytic angina, eleven cases; so-called monocytic angina, one case; aleukia, two cases; symptomatic agranulocytic angina in septic endocarditis, two cases, and symptomatic agranulocytic angina in septic (streptococcic) anemia, one case.

Of particular interest were the necrotic ulcerative affections of various mucous surfaces, so commonly observed in connection with agranulocytic syndromes. The gangrenous processes of the

mucous membranes were localized mainly in the mouth and involved its various structures, such as the gums, tonsils, soft palate, lips, and buccal mucous surface, and in one case the nose. This condition raises the question as to whether the ulcerous gangrenous processes were primary or developed as secondary manifestations of the agranulocytic complex.

It would seem that the onset in some cases is a simple tonsillar angina (streptococcic?) or a more or less severe streptococcic sore throat (rhinopharyngolaryngitis) which is followed by various degrees of bone marrow reactions with subsequent gangrenous processes of the mucous surfaces. Sometimes this gangrenous process is of a secondary nature resulting from hemorrhagic infiltrations and infarction of the nasal and oral mucous membranes.

This condition may be likened to the neutropenic hypoleukocytic blood picture in some instances of acute phlegmonous gangrenous appendicitis incited by hemolytic streptococci.

A sore throat antedated the onset by a few days or weeks in seven instances, while sinus (ear) trouble was found mentioned four times by the patients as having preceded their present severe illness for a short time. Sudden onset was definitely established in three cases.

In the eleven instances of agranulocytic angina, icterus was observed twice and hemorrhagic purpura four times.

As to the bacteriological investigations, in seven cases streptococci were observed, twice in smears from the local ulcerous-gangrenous areas of the mouth. In one case, streptococci were obtained from the local lesions and from the urine. In five cases, in which autopsies were performed, a hemolytic streptococcus was cultured from the splenic pulp.

In eleven instances the behavior of the blood platelets was investigated and a thrombocytopenia of more or less marked degree was detected in eight cases. In two instances of the so-called agranulocytic angina, the blood platelet count was within the lower boundary of normal thrombocytic values. One case of recrudescent septic endocarditis, appearing clinically under the picture of an aleukia, was characterized by a complete absence of the blood platelets (athrombocytosis).

Postmortem examinations were performed in seven instances, and in each a toxic or septic picture was disclosed. The reaction of the spleen was found to depend upon the predominence of the toxic or septic symptoms; in the latter instance enlargement of the spleen was present. In cases observed at autopsy, a splenic tumor, partly of septic character, was disclosed five times.

DISCUSSION

It is interesting to note that abundant hemorrhages from the necrotic ulcerous tissues, particularly from the uterus and vagina, nose, and other mucous surfaces will aggravate an already existing anemia.

The thrombocytopenia and athrombocytosis, if accompanied by quantitative and qualitative changes in the leucocytic values, are significant manifestations of an intense septic damage to the bone marrow.

In some agranulocytic cases, the qualitative analysis of the peripheral blood will disclose an increase in monocytic blood elements, occasionally presenting the picture of a pronounced mononucleosis. The monocytic reaction is a peculiar, pathological bone marrow reaction, which results from a disturbed leukopoesis due to infectious or toxic influences upon, or irritations of, the bone marrow. The so-called monocytic angina (Schultz) belongs to this group.

We had opportunity to observe accurately and study four cases of benzol poisoning, characterized from the beginning by a sharp drop in the leukocytic counts accompanied by a considerable decrease in the number of polymorphonuclears. It clearly appeared that the leukopenic and granulocytopenic values were running parallel, namely, the more pronounced the decrease in the number of the white blood cells, the more scarce were the granulocytes. Hyperchromatic anemia of regenerative type and thrombocytopenia completed the hematological data. We did not observe in these instances any septic temperatures nor gangrenous conditions of the accessible mucous surfaces, at the beginning. One of these cases showed, however, as a terminal event, severe hemorrhages from the nose, mouth, and vagina, and,

shortly before death, development of an ulcerous stomatitis and gangrenous mastitis with septic temperature and profound anemia, a clinical picture very similar to and suggestive of an aleukia.

The agranulocytic leukopenia, which is characteristic of the blood of individuals suffering from benzol poisoning, appears to be the result of direct damage to the leukopoetic system (central deleterious action: osteomyelotoxic), while leukocytolytic processes (peripheral destruction) seem to occur also. In view of simultaneous injurious effects upon the erythropoetic system, it is plausible to conclude that the benzolic agranulocytosis is mainly a primary bone marrow damage due to osteomyelotropic properties of benzol. This dangerous poison first inhibits and then paralyzes the bone marrow functions.

The various pathological reactions of the leukopoetic and erythropoetic systems, encountered in instances of elective action of damaging agencies of toxic and infectious nature upon bone marrow, as found in the morphological blood picture, are of great symptomatic value and have been summarized as follows, omitting completely the behavior and reactions of the lymphatic apparatus:

1. Neutrophilic (hyper-) leukocytosis
2. Neutropenic white blood picture (normal leukocytic values)
3. Neutropenic hypoleukocytic reaction
4. Agranulocytosis with leukopenia
5. Myeloblastic leukemic reactions

The agranulocytosis may be accompanied by toxic aplastic anemia, toxic hemolytic anemia, or by a normal erythrocytic blood picture. The thrombocytes may show normal values or they may be markedly decreased (thrombocytopenia) or completely absent (athrombocytosis).

CONCLUSIONS

Our cases are characterized by a toxic elective action upon the leukopoetic system with destruction of granulocytes and concomitant abnormal reactions of the bone marrow, processes which

manifest their presence by quantitative and qualitative changes of the peripheral blood.

The elective action upon the bone marrow tissues, the osteomyelotropic action, explains also the often observed damages to other functional parts of the bone marrow, to the erythropoetic system and to the thrombogenesis, with resulting anemia and thrombocytopenia. We are confronted thereby with a complete destruction, anatomical and functional, of the blood forming tissues, as a result of deleterious influences of some toxic and infectious agencies.

The hematological picture is initiated by transitory functional disturbances of the bone marrow, followed by progressively developing damages and increasing destruction of its tissue, with subsequent total, fatal elimination of its entire function, involving all its functional units and vital activities (leukopoesis, erythropoesis, thrombocytopoesis).

From the morphological behavior of the peripheral blood, we can quite positively conclude in a given case the character and extent of the pathological-physiological disturbances and alterations of the affected bone marrow.

The variations in reactions are pathological functional expressions of individual character, of a constitutionally weak, functionally readily insufficient and easily vulnerable bone marrow, depending also upon the type and virulence of the noxious agent.

The constitutional (functional) inferiority of the bone marrow is vividly expressed in those instances in which an increased functional demand is urgently and vitally needed, but the bone marrow tissues respond with an alarming collapse and a rapid, complete exhaustion.

STUDIES ON SCHILLING COUNT IN APPENDICITIS*

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A review of recent literature shows a striking lack of confidence by surgeons in the blood count as an aid in the diagnosis of appendicitis. It is interesting to note that men like Deaver and Woodall discuss this subject without mentioning the leukocyte count; Lincoln claims it to be an unreliable sign in either diagnosis or prognosis; Reese states, "to these symptoms may be added leucocytosis, which, however, is totally unreliable"; Bolling derives no information therefrom; and neither Wallace, Koritschoner, Hinton or Jackson are impressed by the count as a dependable sign, even questioning its value in diagnosis. Many authors, among whom are Smith and Brooks, report normal blood counts in cases with severely infected appendices.

In many instances, only the total white cell count is considered; others consider the relationship of the total cell count to the percentage of polymorphonuclears, some using various charts or indices of resistance to illustrate this relationship more graphically. This lack of accord in interpreting the leukocyte count led Hellwig in 1928 to conclude that, "Fowler's opinion that it is difficult to estimate the exact diagnostic value of the leucocytosis is at the present time as true as it was in 1900." From such a study of the literature, one inevitably carries away the impression of a striking lack of understanding by the surgeon of the present day concept of the physiology and pathology of the blood as determined by the total and differential cell counts.

A review of the development of the blood count and of the theories of its interpretation may help to explain the reason for this chaos. The first enumeration of the cellular elements of

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the blood was made, in 1851, by K. Vierordt.[10] Erlich's introduction, in 1879, of staining methods for the study of blood smears made possible the separation of leukocytes into classified types, and initiated a new epoch in the study of hematology. Einhorn[10] is credited with the first differential cell count from a smear, in 1884, but his interest was in the technic of the count rather than its interpretation. In 1905, Sondern concluded from a study of the results of a large number of blood counts rather than from theoretical reasoning, that, "the increase in the relative number of polynuclear cells is an indication of the severity of toxic absorption and the degree of leucocytosis is an evidence of the body resistance toward infection." These observations were immediately confirmed by Gibson, who evolved a chart showing this relationship graphically. Wilson modified Gibson's chart by the addition of a line of resistance. In 1919 Walker verified the work of Sondern, Gibson and Wilson and presented a mathematical formula, the index of resistance, which was, "a ready and tangible method of determining the degree of resistance and which expresses essentially the same thing as Gibson's chart, but is a more accessible means of interpreting a blood picture than the standard chart." These writers noted exceptions in children to whom Gibson's resistance chart did not apply because of the variations in the normal leukocyte count from that of the adult, and by Sondern, "in conditions in which pus is confined so that no toxic absorption occurs or when the purulent exudate is of tuberculous or typhoid origin." More recently, Menninger and Heim, and Kilduffe, in 1924, and Jones and Crocher, and Neal and Robnett, in 1927 concur in a general way in the above conclusions.

In 1904, about the time Sondern was carrying on his observations, Arneth attempted to gauge the severity of infections by the study of blood smears. His discovery that variations in the nuclear structure of polymorphonuclear cells corresponded with the severity of the infection was epochal and far reaching. The observed variations in nuclear structure he grouped into classes according as they contained "one or more nuclei," meaning nuclear lobes. By this method of classification, the cells fell into

five groups which were further subdivided according to nuclear conformation, so that in all twenty distinct neutrophilic forms were listed. His work awakened a more than transitory interest both abroad and in this country, but the method was so cumbersome and time-consuming that its practical application was discouraged, in spite of the fundamental deductions possible from its use.

However, Arneth's work opened the path for further studies along this line, and in 1914 Cooke[7] described a method for making the differential count which, though separating the neutrophiles into five distinct classes, made no further subdivisions. He also was more specific than Arneth in his basis of classification so that the personal equation factor of error was diminished. In using the Arneth classification, great difficulty was often encountered in deciding on the presence, and extent, of lobulation according to this author's notions; Cooke's classification led to less uncertainty by his criterion that, "if there is any band of nuclear material except a chromatin filament connecting the different parts of a nucleus, that nucleus cannot, for the purpose of the count be said to be divided." While this method eliminated some of the objections to the Arneth count, it never came into popular use as it also was rather cumbersome, and its expression by various mathematical devices, known as weighted means, did not lend it to ready interpretation.

Schilling in 1912 translated the work of Arneth into anatomical terms and still further simplified the classification by dividing the granulocytes into the following classes:

1. Myelocytes, cells with completely round nuclei; granulocytic primary cells which are normal cells of the bone marrow and are never found in the normal blood picture.
2. Young form neutrophilic leukocytes or metamyelocytes of Pappenheim having slight nuclear indentation.
3. Band or stab forms in which no true nuclear lobulations can be distinguished but where the nucleus has a long narrow or bent form.
4. Cells with definite nuclear segmentation.

Schilling describes degenerative and regenerative shifts which he interprets as indicating the state of bone marrow function.

Let us now look into this question of the bone marrow as an organ of leukopoesis and see how an understanding of its physiology and pathology fits in with the views of Arneth, Cooke and Schilling. The polynuclear granular leukocytes under normal conditions are formed exclusively in the bone marrow. They develop by a process of maturation from the fixed reticular cells of the bone marrow and pass through the intermediate stages of myeloblast, promyelocyte, myelocyte and metamyelocyte in the bone marrow, and are delivered to the blood stream after maturation of the metamyelocytes into young leukocytes. These leukocytes become more mature in the circulating blood as shown by Ponder. The maturation here is no longer a process of cell division, but of nuclear segmentation. Finally there is a loss of motility and the cells become fragile, die and are removed from the circulation.

The entire structure of the functioning bone marrow in man is in a relatively uniform state, that is, the proportions of different levels of maturation are relatively constant.[24] The delivery of young leucocytes from the bone marrow is based on rhythmic orderly division and maturation.[25] Shaw has shown two tides in the volume of neutrophilic leukocytes delivered to the circulation, each occupying approximately twelve hours. The day tide begins in the forenoon, reaches its flood during the afternoon, and completes its ebb in the evening. The night tide starts in the evening, attains its height in the hours after midnight, and ebbs away in the early forenoon. These tides are not influenced by food, exercise or sleep. He also shows that the average daily variation in the total number of leukocytes is from 40 to 56 per cent in twenty-four hours, but that the percentage of cell types in the differential count is subject to but little variation.

Ponder aptly designates this condition of cell class stability as "the steady state" and claims that the Arneth count represents an equilibrium between cell production and cell destruction. Sabin groups leucopoetic activity into two classes, maturative and chemotactic, ordinarily one keeping pace with the other so that the proportion of young cells shows no marked fluctuation. Arneth and Schilling have shown that normally 4 to 5 per cent

of immature leukocytes are present in the blood stream and that this percentage is not influenced by the tide or so-called physiological leukocytoses.

Buchner and others endow bacterial proteins with chemotactic properties. Bacon, Noy and Eppler believe that the stimulus to increased bone marrow activity comes from the altered body protein due to hydration, and that in infection there is an increase of the substances in the body that afford the normal stimulus. Sabin sees the infecting bacteria as introducing both a chemotactic and maturative factor when a leukocytosis results, and a chemotactic factor alone when a leukopenia follows a temporary leukocytosis.

In mild infection maturation keeps pace with chemotaxis so that there is no marked increase in immature forms in the circulating blood. As the infection becomes more severe, maturation cannot keep up with the demand for leukocytes, so that an increasingly greater number of immature cells appear in the blood. Finally, in severe, overwhelming infection when all the metamyelocytes have been withdrawn from the bone marrow, the myelocytes enter the circulation and the total count drops.

With this clarified understanding of the physiology of the bone marrow and its reaction towards infection, it seems logical that a blood count which mirrors the condition in the bone marrow should interpret the severity of the infection more accurately.

In a previous paper[37] data were submitted on a series of non-infective conditions in which the total leukocyte count varied from 6000 to 15,000 and the polynuclear neutrophile count from 57 to 78 per cent, with a range of 3 to 5 per cent of immature forms. A group of secondary anemias with so-called relative leucocytosis showed from 2 to 5 per cent of immature leukocytes. A series of non-suppurative infective conditions such as acute arthritis, cervical adenitis, cholecystitis, ulcerative colitis, and so forth, gave immature counts of 7 to 12 per cent. On the other hand, in suppurative processes the immature cells amounted to more than 14 per cent. In the above study all of the members of the three immature groups of Schilling were combined under the heading of immature forms. This was done for the purpose of

simplification, both for the technician who made the count, and for the clinician who interpreted it. Although some of the sensitivity of the Schilling count is apparently lost by this procedure, we always take into consideration the degree of shifting to the left—towards the myelocytes—when interpreting the count.

A study of the value of this type of blood count in appendicitis was undertaken for two reasons; first, because in this condition the blood count is very often relied upon for aid in diagnosis, and secondly, because the count could be checked by pathologic material and its worth more readily evaluated.

TABLE 1

671 Cases of Appendicitis—Schilling Counts

HISTOLOGIC DATA	NUMBER OF CASES	TOTAL LEUKOCYTE COUNT	PERCENTAGE OF POLYNEUTROPHILES	PERCENTAGE IMMATURE GRANULOCYTIC FORMS	AVERAGE PERCENTAGE OF IMMATURE GRANULOCYTIC FORMS
				per cent	
1. No evidence of active inflammation	277	6,400–14,600	55–83	2–8	4.3
2. Catarrhal appendicitis	180	8,000–18,200	67–83	7–14	10.2
3. Acute diffuse suppurative appendicitis without perforation	188	10,000–22,800	70–89	14–28	17.8
4. Acute diffuse suppurative appendicitis with perforation and peritonitis	26	11,800–30,800	69–92	32–47	39.5

DISCUSSIONS OF CASES

The material surveyed consists of 671 patients whose appendices were removed at the Newark Beth Israel Hospital from April 1, 1929 to April 1, 1930 and in whom cell counts had been done preceding the operation. These counts were reported as usual without any regard for the percentage of immature cells. All the slides used in making the counts were numbered and filed for future Schilling count. The appendices were sectioned and reported using the following classification:

1. Appendices showing no evidence of any active inflammatory process (including normal, healed, and obliterated appendices).
2. Catarrhal appendicitis, with the inflammatory process limited to the mucosa.
3. Acute diffuse suppurative appendicitis without perforation, with or without gangrene.
4. Acute diffuse suppurative appendicitis with perforation and peritonitis.

In the first group were included 277 cases (table 1). The total white count varied from 6400 to 14,600. The polyneutrophile percentage from 55 to 83. The Schilling count ranged from 2 to 8 per cent immature forms with an average of 4.3 per cent. It is interesting to note that in the cases in which the Schilling count was above 5 per cent, a temperature increase with some evidence of mild infection was clinically present, although the appendix was histologically free.

There were 180 appendices diagnosed histologically as catarrhal appendicitis studied. The total white count in this group ranged from 8000 to 18,200; polyneutrophiles 67 to 83 per cent; immature forms 7 to 14 per cent with an average of 10.2 per cent. The appendices in the patients with 14 per cent immature cell count showed beginning edema and exudation in the muscularis, but not of sufficient degree to justify a diagnosis of acute diffuse suppurative appendicitis.

One hundred eighty-eight cases of acute diffuse suppurative appendicitis without perforation and with or without gangrene showed total white cell counts ranging from 10,000 to 22,800, with polyneutrophiles from 70 to 89 per cent; immature forms 14 to 28 per cent with an average of 17.8 per cent. The immature forms seemed to follow definitely the severity of the histologic process and those cases with gangrene showed the higher counts.

Because of the fact that many of the patients with acute suppurative appendicitis with perforation and peritonitis were admitted for emergency operation, having had a blood count before entering the hospital, only twenty-six cases in this group were studied. These showed total white counts of from 11,800 to 30,800; polyneutrophiles 69 to 92 per cent; immature forms 32 to 47 per cent, with an average of 39.5 per cent.

It may not be amiss to quote here a few cases in which the blood count by the usual method was wholly misleading and in which a Schilling count would have revealed the true picture.

Case 1. A male, aged fifteen years was admitted with a history of colicky pains not associated with nausea or vomiting for an indefinite period of time. On the afternoon before admission he experienced cramp-like pains in the right lower quadrant which did not radiate and were not associated with nausea or vomiting. On admission to hospital, the temperature, pulse and respirations were normal. The abdomen was soft and flat except for resistance and tenderness in right lower quadrant. Blood count showed 10,000 white cells with 70 per cent polyneutrophiles. A clinical diagnosis of catarrhal appendicitis was made and the patient was operated upon the next morning, when an acutely inflamed appendix was removed showing acute diffuse suppuration microscopically.

This case is presented as illustrative of a group of cases of acute appendicitis in which the blood count, as done routinely, may not only be of no definite help in the diagnosis, but may even be somewhat misleading. In considering the blood count in the above case together with the almost negligible clinical data, the surgeon was warranted in waiting until the next day for routine operation. However, a Schilling count done later on the same smear showed 14 per cent immature cells among the 70 per cent of of neutrophilic granulocytes, definitely indicating a suppurative process. Had the Schilling count been taken into consideration, the patient would probably have been operated upon immediately. The histologic study in this case showed a well advanced suppuration with exudate covering the serosa. The convalescence of this patient was rather stormy.

Case 2. A male, aged 49 years, gave a history that one day before admission to the hospital he was suddenly seized with sharp pains in the right side of the abdomen after which he vomited several times. The pain persisted, keeping him awake all night. Upon admission to hospital the next morning, patient still had pain and suffered marked discomfort. Examination showed a distended abdomen with muscle spasm throughout, especially in the right lower quadrant and rebound tenderness in this region. The temperature was 100; pulse 100; and respirations 20. Blood count showed 11,800 white cells with 69 per cent polyneutrophiles. Operation was performed immediately in spite of the blood count and free pus was found in the abdomen. The appendix was markedly thickened, covered with a heavy exudate and ruptured at the midpoint. Two cigarette drains were inserted.

In this instance the blood count was entirely misleading, showing a descending line according to Gibson's and Wilson's studies, whereas a Schilling count showed 47 per cent of immature cells among the 69 per cent polyneutrophiles. Many of these immature forms were myelocytes, showing a marked shifting to the left. This should have definitely led to a diagnosis of severe infection and to the suspicion, at least, that peritonitis had already complicated the picture.

From the above study one gains some rather definite impressions as to what can be learned from this type of count. In the presence of a normal immature count, I agree with Cooke[6] that an inflammatory process in the appendix can be definitely excluded. When the immature count is below 14 per cent I feel quite certain that there will be no diffuse appendicitis and that the inflammation is limited to the mucosa and has free drainage. With immature counts of more than 14 per cent immediate operation is always recommended and as the count approaches 25 to 30 per cent, gangrene of the appendix or localized peri-appendicitis is the invariable pathologic finding. When the percentage of immature cells reaches 35 or more, the diagnosis of ruptured appendix with peritonitis is almost always correct.

Repeated counts following operation in these cases give a reliable index as to prognosis. A return towards normal in the number of immature forms indicates a subsidence of the infection. A maintained high Schilling count should be interpreted as persistence of infection, probably with a localized inflammatory process about the stump or the cecum. A rising Schilling count is of very serious prognostic import and usually indicates a peritonitis. If there is a rise in immature cells after several prior counts had shown a recession in the immature cells, it indicates some complication, and according to Reznikoff, serves to detect this complication before it is clinically apparent.

SUMMARY

The methods in vogue at the present time for interpreting the leucocyte count in the diagnosis of appendicitis are not satisfactory as evidenced by the literature. The degree of leuko-

cytosis itself is of no value due to physiological factors, such as the diurnal tide of Shaw, migration of leukocytes into the tissues, and redistribution of cells in the peripheral circulation as spoken of by Mirkin and Rachlin. The differential cell count giving the percentage of polymorphonuclear leukocytes and the relation of this percentage to the total leukocyte count, according to Gibson's standard chart and Walker's index of resistance, contributes valuable information as to the patient's resistance to infection in many instances, but cannot be interpreted into terms of pathologic lesions. The response of the body to infection through the leukocytes is a matter of bone marrow function. Sabin and others have shown that the correspondence between bone marrow and blood are relatively exact insofar as cell picture is concerned. The Schilling count is an interpretation of the blood picture in terms of bone marrow function.

CONCLUSIONS

From a study of 671 cases in which the Schilling blood picture was correlated with the histologic observations in the appendix, I conclude:

1. That the presence of a normal percentage of immature forms rules out appendicitis.
2. That an immature count of less than 14 per cent indicates a mild process, probably limited to the mucosa.
3. That an immature count of more than 14 per cent indicates a diffuse suppurative appendicitis, of increasing severity as the count approaches 30 per cent.
4. That more than 35 per cent of immature cells indicates perforation, with peritonitis.
5. That repeated counts are of definite prognostic value.

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HEMORRHAGE WITH SUDDEN DEATH IN TRACHEO-BRONCHIAL LYMPH NODE TUBERCULOSIS IN ADULTS*

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Current medical literature emphasizes the importance of tracheo-bronchial lymph node tuberculosis in adults. Many are convinced that the problem of pulmonary tuberculosis in adults arises largely from the extension of the disease to the lungs and pleurae from some focus in the nodes at the hilus. The autopsy and the roentgenogram have taught us how frequently these nodes in adults are infected with tuberculosis without the production of the disease. It is recognized that tuberculous disease in children is essentially of this type. Chandler and Preston pointed out that the great frequency of tuberculosis of the mediastinal nodes "must be accepted as an established fact, for in many series of autopsies performed on tuberculous children, the bronchial glands are affected in nearly a hundred per cent. of the cases, the tuberculous disease here being commoner than in any other part."

Tuberculosis of the tracheo-bronchial lymph nodes is more difficult of clinical demonstration in adults than in children, because of the absence of reliable physical signs. Nevertheless, Pratt and Bushnell declared that "only through the instrumentality of the lymphatic system" can there be a sufficient "collection of tubercle bacilli with their poisons" to produce tubercle formation "in the relatively immune individual." We are aware that normal lymph nodes at the hilus do not cast shadows in the roentgenogram.[3] Dense foci indicating calcium deposition are accepted universally as evidence of old tuberculous infection in

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these nodes. Opinions differ with regard to the detection in the x-ray film, of caseation in the tracheo-bronchial nodes, although evidence of caseation indicates that the tuberculous process is not arrested completely. However, I am of the opinion that dense shadows at the hilus which are irregular in contour and in the variations of density within the shadow, represent lymph nodes in which incomplete calcification is associated with caseation. These shadows are usually larger than the clear cut, sharply defined, deep density of completely calcified foci.

In children, tuberculosis of the tracheo-bronchial lymph nodes is associated frequently with rupture of these nodes into the blood vessels, pericardium, esophagus, trachea and bronchi.[4,6] Among adults, such occurrences sufficiently destructive to cause sudden death, must be rare. The literature calls attention to this possibility, but so far, reference has been found to only one other specific instance. Hartman, in 1925, reported the case of a colored woman in whom sudden death occurred by hemorrhage. The autopsy revealed the erosion of the trachea and innominate artery by unsuspected tuberculous infection of the tracheo-bronchial lymph nodes.

Three cases of sudden death in adults by hemorrhage due to the erosion of pulmonary vessels in tuberculosis of the tracheo-bronchial lymph nodes, are reported here.

Case 1. A male negro, aged thirty-three years, entered the hospital after an illness of three months, "for treatment of left spontaneous pneumothorax and pleurisy with effusion." This diagnosis had been substantiated by previous x-ray examination of the chest. No lesion in the lungs had been noted in the x-ray report, nor detected in the previous physical examination. Upon the entrance of the patient to the hospital the provisional diagnosis of pulmonary tuberculosis was made. The temperature was 98.6°F., the pulse 84 and the respiration 20. There had been a loss of weight from 175 pounds to 159 pounds within a year. The chief complaints were cough with expectoration, hoarseness, headache, pain in the left chest, weakness and easy fatigability. The admission date was August 15, 1927, 2:10 p.m. The patient was given the routine care for new patients and his condition appeared "fairly good." Hemorrhage from the nose and mouth began at 2:30 a.m., August 16, twelve hours after admission. The patient had arisen and gone to the lavatory. Paliative treatment failed to check the flow of blood and in twenty minutes he was dead.

At the autopsy the organs were found bloodless. Easily torn fibrous adhesions were present between the visceral, parietal and interlobar pleura on the right. Gross examination of the right lung revealed no pathological lesion. The left lung was described as follows: The left lung fills the left half of the chest completely, is almost black in color, friable, and has the appearance, weight and consistency of liver. Only a very few fibrinous, easily torn, pleural adhesions are present. The lung is several times heavier than the right and pieces of it sink in water. The organ cuts like liver. The cut section possesses a porous rubber sponge-like appearance. The upper lobe and the upper portion of the lower lobe are dark scarlet. The remainder of the lower lobe is black and densely solid without porosity. The blood vessels are engorged. Their walls are bright red. Repeated section and dissection fail to reveal any primary site of pathology. An incision through the hilum discloses an encapsulated, confluent mass of caseous and calcareous lymph nodes. This focus occupies the angle between the trachea and the left bronchus and has a diameter of 3 cm. The nodes included within the thick, fibrous capsule have lost their identity and form a single degenerated, cheesy, calcareous mass which is easily shelled out. The lower border of the capsule is in juxtaposition to the left descending bronchus and branch of the pulmonary artery. An opening large enough to admit the tip of the index finger, connects the encapsulated mass with the lumens of artery and bronchus. No gross pathological lesions were found elsewhere. Microscopical examination of the apex of the right lung revealed miliary tubercles. These were not numerous and consisted largely of lymphoid cells interspersed with fibrous stroma and a few polyhedral cells. Only an occasional center appeared necrotic.

Case 2. A male negro, aged thirty-five years, entered the hospital on May 24, 1928, complaining of cough, spitting of blood, night sweats, and loss of weight. Temperature ranged from 97°F. to 103°F., pulse 80 to 120, respiration 20 to 35. Physical examination elicited increased fremitus, dullness, whispered pectoriloquy and whispered voice. Breath sounds were broncho-vesicular. Râles were present. The x-ray showed infiltrations and consolidations with a large cavity in the left apex. Four out of eight sputa were positive. The blood Wassermann was negative. The course of the disease was associated with repeated hemoptysis. Death followed a hemorrhage on June 11, 1928.

At autopsy the lungs were described as follows: The hilus lymph nodes are greatly increased in size, are soft, black and caseous. The largest is 4 cm. long. The left lung is adherent at the apex and base. The lung is soft, crepitates and floats. On cut section, fibrous scars appear in the apex. Small, discrete, caseous areas are scattered throughout all lobes. Numerous, large, caseous lymph nodes appear along the course of the bronchi and blood vessels. The right lung is free, pink, soft and crepitates. On cut section there is emphysema in the upper lobe. The middle and lower lobes are red and moist, with small, raised, irregular, scarlet areas about the bronchi. The nodes along the bronchi and blood vessels are likewise large and caseous. Along the course of the bronchus and pulmonary artery of the right middle lobe, several of these caseous nodes appear. One has eroded through the walls of both bronchus and artery.

Case 3. A male negro, aged thirty-seven years, was admitted to the Hospital January 14, 1928. He had "caught cold" in January, 1927. Since then he had complained of cough, shortness of breath and "spitting of blood many times." *Mycobacterium tuberculosis* were found in the sputum; the blood Wassermann showed a two plus reaction. The x-ray disclosed numerous infiltrations and irregular areas of consolidation throughout the upper portions of both lung fields. On November 20, 1928, he left his ward without permission, jumped a fence, and died in ten minutes from pulmonary hemorrhage.

The autopsy revealed a moderately advanced pulmonary tuberculosis, bilateral tuberculosis of the mediastinal lymph nodes and erosion of a branch of the pulmonary artery in the right middle lobe, by a caseous lymph node.

Three cases of sudden death in adults by hemorrhage due to the erosion of pulmonary vessels by tuberculosis of the tracheobronchial lymph nodes, are sufficient to call attention to the possibility of such an outcome. The deaths reported occurred within fifteen months. In the first patient no definite, clinical evidence of pulmonary tuberculosis had been observed. There had been no previous spitting of blood. In the second and third patients, pulmonary tuberculosis had been demonstrable and was associated with blood in the sputum. Neither had been seriously ill, however, and it is evident that for them, the infection in the lymph nodes was more serious than the pulmonary invasion.

It is striking that all four cases have occurred in negroes. This raises again the question of the character of the tuberculous infection in negro adults. Does tuberculosis in negroes tend to conform to the juvenile type, rather than the adult type usually observed in whites? This much may be stated, that in a series of over 200 autopsies upon adult male negroes dying of tuberculosis, gross evidence of massive infection in the tracheo-bronchial lymph nodes, has been observed in every case.

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THE INFLAMMATORY NATURE OF NODULAR GOITRE AS A CHRONIC THYROIDITIS*

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The purpose of this paper is to present the conception that many of the nodular thyroid glands should be considered as being inflammatory rather than as tumors. This is a part of a critical study of 1000 thyroid glands over a period of eight years. These cases represent the routine hospital admissions for thyroid diseases from the fringe of the goitrous region in central Pennsylvania. The cases include all forms of thyroid disease with the nodular types making up more than one-fourth of the group.

There is no doubt that the pathology of the thyroid gland, while it follows the laws of reactions elsewhere in the body, has its own individualities. Applying a general knowledge of histological pathology to the first hundred cases one studies and following the general outline of textbooks, one considers at first many cases of tumor and too large a number, possibly malignant. Then, as more and more sections taken from different parts of the same gland are studied, the picture with its wide variations becomes more confusing. It gradually dawns on one that these reactions are not all hyperplasias but something else. What this something else may be becomes quite clear when all structures in the glands are taken into consideration. From this standpoint the pictures are those of inflammation.

It is necessary to define my conception of hypertrophy, hyperplasia and inflammation. An hypertrophy is an increase in numbers of cells and size of a part associated with an increase in function. An hyperplasia is an increase in numbers of cells and size

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of a part without necessarily increase in function. Indeed, there is often the reverse in hyperplasia—a decrease in function. An inflammation is a reaction on the part of the tissue to a stimulus. The stimulus may be anything but must be present. The reactions follow definite laws of transudation, exudation, degeneration, regeneration and hyperplasia.

I realize that large numbers of cases give a valuable experience but Osler once said ten beds well studied are worth more than the prefunctory rounds of a hundred. This study is based on only one thousand cases but it represents the milling over of available data over a period of ten years. A complete redigest of the histories, gross specimens and microscopic slides was made after the conceptions as set forth in the paper were reached. This has afforded a uniformity of conclusion. Every gross specimen which had been labelled and stored was reviewed and again briefly described to be compared with the full report. All available microscopic slides were restudied. These briefs were then put together and the tabulations made at one time. The conceptions, of course, were the result of gradual rearrangement of ideas as the years went by.

In reviewing textbooks and the literature a great deal of confusion exists as to just what is meant by the types enumerated and each man who has studied the question has devised a nomenclature to meet his needs. Others have combined classifications and as a result hardly two authors agree as to either clinical or pathological classifications. In addition, errors creep in and are perpetuated. For example, Riedel described his firm type of thyroid as "eisenharte" (iron hard). This is variously described as Riedel's thyroiditis, Riedel's thyroid tumor and worst of all, as Eisenhart's strumitis.

The pathology of the thyroid gland as seen in operative specimens, has been greatly altered by the widespread use of iodine. This factor must be considered from now on in any study of the relationship of the actual pathology and the disease entity as compared with the years before iodine therapy. Fortunately, most of my own work was carried on before the use of iodine, and represents, therefore, the actual and not the altered pathology of the gland.

TABLE 1

PATHOLOGICAL CLASSIFICATION OF THYROID DISEASES

I. Normal thyroid. No pathological changes.
II. Anomalies.
    1. Absent.
    2. Accessory.
III. Atrophy.
    1. Congenital deficiency (Type: cretinism and myxedema).
    2. Senile.
IV. Metamorphoses. Alone or part of complex reactions.
    1. Congestion.
    2. Hemorrhage.
    3. Colloid.
    4. Hyalin.
    5. Amyloid.
    6. Necroses.
    7. Cloudy swelling.
    8. Calcification.
    9. Ossification.
V. Hypertrophy (colloid goitre). Increase in size and function.
    A. Primary hypertrophy (in response to function).
        1. Adolescent.
        2. Pregnancy.
        3. Trophic.
        4. Congenital.
    B. Primary hypertrophy with secondary complex reaction.
        1. Hypertrophy with inflammation.
        2. Hypertrophy with tumor formation.
VI. Inflammations (includes nodular thyroids, many so-called toxic adenomas). All inflammatory reactions.
    A. Acute.
        1. Parenchymatous (exophthalmic goitre).
        2. Degenerative (infectious entities).
        3. Exudative (infectious origin).
        4. Suppurative (abscess and pyemia).
        5. Gangrenous (post-traumatic).
    B. Chronic (nodular).
        1. Productive (enlarged glands, acinal and trabecular increases).
            a. Cellular.
            b. Fibrous.
            c. Colloid.
            d. Cystic.
            e. Calcareous.
            f. Osseous.

TABLE 1—*Concluded*

VI. Inflammations—*Concluded*
- 2. Contractive (small glands, atrophy, fibrous contraction, calcium and bone).
  - a. Fibrous.
  - b. Cystic
  - c. Calcareous.
  - d. Osseous.

C. Specific.
- 1. Tuberculous.
- 2. Syphilitic.

VII. Neoplasm.

A. Benign.
- 1. Adenoma (acinal, interacinal (Wolfler) epithelial origin. Pure tumors.)
  - a. Single.
  - b. Multiple.
  - c. Cystic.
  - d. Colloid.
  - e. Degenerative.
  - f. Foetal.
- 2. Adenoma with thyroiditis.
- 3. Fibroma (trabecular connective tissue origin).
- 4. Teratoma and dermoid cysts.

B. Malignant.
- 1. Carcinoma.
  - a. Simplex.
  - b. Adeno.
  - c. Papillary.
- 2. Sarcoma.
  - a. Round and spindle cells.
  - b. Endothelioma.
  - c. Perithelioma.
  - d. Myxosarcoma.

VIII. Parasitic cysts (Echinococcus).

With this explanation and in order to fix definitely the type of thyroid with which this paper is concerned, it is necessary to present a pathological classification (table 1). I do not wish further to cloud the situation, of which I have just complained, but desire to present the beginning of what might be taken for the structure of a classification. Any complete pathological study must be detailed because of the different types of tissue concerned. This

does not preclude a more simplified form for clinical usage which I have also included as a guide. I know that both these lists can be improved and I have changed them many times. They offer, however, a very satisfactory means of definitely cataloging the same general types of cases. A more detailed report on this classification will appear later.

The present paper is concerned with classification of chronic thyroiditis either productive or contractive. Many of the nodular types of goitre, about half of which are toxic, are not true tumors but are phases of an inflammatory reaction. It is true that areas of epithelial hyperplasia are to be found in certain parts of the gland but the predominating changes in the supporting structure are inflammatory with epithelial regeneration and degeneration and associated accumulations of colloid. To my mind the accumulated colloid is an innocuous vehicle for the storage and dilution of the thyroid active principles just as mucus is an innocuous lubricant and vehicle. While the thyroid gland is a so-called ductless gland, in reality the relationship of the acinal epithelium histologically with the surrounding capillaries makes it almost a sponge squeezing its product into the blood stream. It must have something to withhold its activity during periods of overproduction as in the case of the gall bladder for the liver.

The colloid acts as the material of storage. When this delicate mechanism is interfered with either by demands of function or by an outside stimulus changes occur in the stroma as a result of the stimulus and in the epithelium as an activity or degeneration and clinical symptoms result. This mechanism originated within or without the thyroid gland, fits in perfectly with that of other so-called ductless glands such as the adrenal.

In this series the different types of glands were divided according to the chart. Twenty-nine (3.3 per cent) glands were considered pathological normals, one hundred twenty-two (14.2 per cent) were pure primary hypertrophies, (Marine's type of colloid goitre), one hundred fifty-one (17.6 per cent) were hypertrophy with secondary thyroiditis. The pathological changes began as a pure hypertrophy and progressed through stages of inflammatory reaction. These are the nodular types of chronic goitres of long

TABLE 2

INCIDENCE BASED ON MODEL CLASSIFICATION SUBMITTED

	NUMBER	TOTAL FOR GROUP	PERCENTAGE BASED ON 862 GLANDS
I. Normal thyroids	29	29	3.3
V. Hypertrophy (colloid goitre):			
A. Primary hypertrophy (all forms)	122	122	14.2
B. Primary hypertrophy with secondary reactions:			
1. Hypertrophy with thyroiditis	151		
2. Hypertrophy with tumor	2		
3. Hypertrophy, thyroiditis with tumor	10	163	18.0
VI. Inflammations:			
A. Acute:			
1. Parenchymatous (exophthalmic goitre)	149		
4. Suppurative	2	151	17.6
B. Chronic:			
1. Productive (all forms)	52		
2. Contractive (all forms)	28	80	9.2
C. Specific:			
1. Tuberculosis	0		
2. Syphilis (histologic evidence)	1	1	0.1
VII. Neoplasms:			
A. Benign:			
1. Adenoma:			
a. Single	187		
b. Multiple	49		
c. Cystic	31	267	31.0
2. Adenoma with thyroiditis	36	36	4.2
B. Malignant:			
1. Carcinoma (all types)	13	13	1.5
2. Sarcoma	0		
Total number of hospital admissions for thyroid diseases	1,028		
Total number of thyroid glands studied	955		
Total number of thyroid glands without reduplication and with all data	862		

duration, two to twenty years, and mostly in females thirty to fifty years of age. They may be either toxic or non-toxic and always give some form of symptomatology. They frequently

begin as a simple hypertrophy (colloid goitre) and are activated to an inflammatory type by pregnancy or some form of stimulus. The epidemic of influenza in 1918 appears often in these histories and very often an attack of sorethroat or some severe infection is recorded. In the third to forth decade they are almost universally associated with dental and tonsillar infections. Clinically they are classed as toxic adenoma and pathologically the only claim they have to being adenoma is the fact that they are nodular and are divided into what appears to be tumors by densely circumscribing trabeculations of connective tissue. There are also all degrees of round cell proliferation, connective tissue formations, active and cellular and inactive and hyalinized. There are blood vessel wall reactions. The acini show all forms of epithelial change from hyperplasia to metaplasia. They vary greatly in size and always have contained masses of colloid. These may be small, variously stained or blood tinged but they are always present. In other words the histological picture taken as a whole is inflammatory and in no sense tumorous. Therefore, I suggest that this group be taken entirely out of the tumor picture, which of course means a different conception of etiology and treatment.

From the incidence data (table 2), it may be seen that eighty (9.2 per cent) of the cases began and continued as inflammatory glands without a preliminary colloid state, that is, nodular thyroids showing all the evidence pathologically of enlargement, nodules, trabeculation, colloid accumulation, acinal epithelial changes, degenerations, fibroses, calcareous deposits, bony changes but not true tumor. This makes 231 (26.8 per cent) nodular thyroids now considered as some form of toxic adenoma which are not tumor but chronic inflammatory reactions. These I have classed as chronic productive and contractive thyroiditis with or without a primary hypertrophy or simple colloid goitre stage. The entire purpose of this paper is to call attention to this conception of a large group, 26.8 per cent, of thyroid glands and further to bring out the importance of etiology and treatment, when this view is held. In other words, chronic infectious bacterial factors associated with necessities for function are playing

a striking etiological rôle. Again, it must be realized and generally recognized that all bacterial reactions in tissue do not necessarily mean suppuration but other types of cellular reaction appear in response to this stimulus. Finally, a true tumor is still a neoplasia associated with hyperplasia.

It is interesting to note in this series of cases that in only two instances did a true tumor as adenoma follow a primary hypertrophy and in only ten did true tumor formation follow the combination of hypertrophy and thyroiditis.

I consider the meaty type of uniformly enlarged thyroid associated with exophthalmus and marked toxicity, familiarly known as exophthalmic goitre, as an inflammation, an acute parenchymatous thyroiditis. In the series there were 149 (17.4 per cent) of this class. This matter will be considered in another paper.

There were only two cases showing suppuration, and it is to this group that the term thyroditis is usually applied.

In my collection there was not a single case of true tuberculosis and only one case of definite histological syphilis. At the same time many cases occurred in persons with chronic lues showing strong positive syphilitic serological reactions.

In the true tumor group usually consisting of well circumscribed meaty tumors in the midst of what was grossly and histologically a normal thyroid, there were 187 as single masses, thirty-nine as multiple masses and thirty-one showing some type of cystic change, in all, 31 per cent of the group. There were thirty-six (4.2 per cent) associated with a previous primary thyroiditis. There were no true fibromata and curiously enough no case of sarcoma. I rather feel that some of the published photomicrographs of sarcoma are of epithelial origin and not connective tissue.

There were thirteen (1.5 per cent) carcinomas. Nine began as primary hyperplasia with adenomatous changes, two were associated with a primary thyroiditis and two showed malignant changes in an adenoma following thyroiditis. I have included in this group only cases of undisputed malignancy.

In reviewing the histories it is interesting to note that when the pathologic types of true tumor, adenoma, are more accurately separated the histories indicate uniformly a non-toxic or very

slightly toxic condition, the toxic types diagnosed clinically as toxic adenoma, falling into the inflammatory thyroiditis group. I would, therefore, like to suggest that the clinical term adenoma is a misnomer, is confusing and should be dropped from consideration as rapidly as possible.

As has been true in the history of nephritis, so with goitre the surgeon and internist cannot be expected to use clinically a complicated pathological classification. I, therefore, propose, subject to future modification, a short clinical classification based on the pathological conceptions outlined in this paper (table 3).

TABLE 3

CLINICAL CLASSIFICATION OF THYROID DISEASES

(Simplified from pathological classification)

The pathological state to be applied to clinical usage only where it is definite and elucidative.

All clinical cases to be divided into:

Group I: Toxic goitre.

Group II: Non-toxic goitre.

and subdivided into subgroups under either group:

A. Thyroid atrophy.

B. Thyroid hypertrophy.

C. Thyroiditis, acute, chronic or specific.

D. Neoplasms benign or malignant.

This places all cases into one of two main groups—toxic or non-toxic goitre. It further distributes them under four main types: (A) Thyroid atrophy, the cretin and hypothyroid group; (B) Thryoid hypertrophy, the single colloid goitres, Marine's type which are certainly not surgical but medical; (C) Thyroiditis, acute or chronic. The true exophthalmic goitres are included under acute throiditis. In this group are included a large number of nodular thyroids uniformly involving both lobes, occurring most often in females, most frequently between thirty and forty, about equally divided between toxic and non-toxic but giving other thyroid symptoms. (D) The true tumors, benign, as adenoma, and malignant, as carcinoma.

The other rare forms of thyroid disease such as tuberculosis,

true syphilis, echinococcus cyst, Chagas parasites, Riedel's thyroid, acute gangrenous thyroiditis are special entities and as such will probably not be accurately diagnosed clinically or pathologically until completely studied.

This shorter clinical grouping offers a definite place for each pathological type of thyroid and is more accurate than the present method of placing the majority in a group most favored by the particular clinician. In this series in the thyroiditis group alone, twenty-six different clinical diagnoses were made by the surgical staff with the vastly predominating group falling under multiple adenoma and such terms as substernal goitre, multiple colloid goitre, colloid adenoma, adenomatous goitre, and so forth, were made. With this multiplicity of terms it is obviously impossible to arrive at any accurate conclusion on the group. On the other hand, if one clinician in speaking of toxic adenoma and another of exophthalmic goitre mean the same type, the confusion is just as bad.

The clinicial picture of chronic thyroiditis varies. The gland is always enlarged above the normal, usually uniformly. Some parts are frequently more involved than others and in the substernal type most of the enlargement may be below the sternum. The gland is predominantly nodular, the resistance is increased over that of simple hypertrophy. In the cystic types fluctuation may be apparent and in the smaller contractive forms the denseness of the calcareous and bony changes may increase the resistance.

The gland in the gross is increased in size, each lobe weighing from 45 to 125 grams. The normal thyroid contour is preserved but the surface is almost always nodular. The capsule is usually thin and smooth but it may be very thick with torn tags as a result of removal. The blood vessels are collapsed but in some cases are very thick and stand out prominently on the surface. This is associated with heavy bands of connective tissue penetrating into the gland along the trabecular lines. The consistency of the gland varies from soft to quite firm, dependent upon the amount of fibrosis present.

The cut surface is always lobulated as a result of fibrous tra-

beculations. The even colloid mosaic of the normal and hypertrophied gland is upset by the irregular fibrosis. The colloid will bulge on the surface in a pebbly way or larger areas may be cystic. Large circumscribed areas of clear or blood tinged colloid may be present. This may be quite fluid and appear as a yellowish-white material. Where areas of acinal hyperplasia are of any size the surface will show spots of fleshy consistence. The calcareous and osserous areas will of course be apparent. In the small contractive types the surface may be very firm and almost beefy. These are to be distinguished from the uniform tumor cases. The characteristic surface shows lobulations of fibrous traceculae sharply defining areas of accumulated colloid.

The microscopic picture will vary with each gland dependent upon the amount and the duration of reaction. The trabeculations will show all types of connective tissue activity from round cells, plasma cells, fibroblasts to heavy hyalinized strands. The latter may be infiltrated with calcium. The bony changes never show any lamella but when decalcified are homogenous masses of structureless material.

The glands show a great variety of change, differences in size, some widely distended with colloid, others contracted. Areas of acinal hyperplasia are seen in the reduplication of lining cells. These are often masses of cells and some areas of new acinal formation but not the uniform hyperplasia of the definite tumors. There is often variation in the picture of different parts of the same gland. Mitotic figures are not the rule in the acinal cells but they may be present. The acini may be very compact and appear as syncytial masses or giant cells. These are not tuberculous but have malignant potentials.

Accumulations of round cells as masses or as a general increase are common. In the very heavy proliferation of these the similarity to a leukemic change is striking. It has always seemed, however, like a specific bacterial reaction. The perivascular spaces at times are filled with round cells.

The acini are often separated into groups, widely distended with colloid. These are walled off by heavy trabeculae of fibrous tissue but without any fibrosis whatsoever between the affected acini.

The staining reactions of the colloid varies within wide limits. This has all been carefully described.

Congestion of blood vessels is not the rule but in some cases this is marked with areas of hemorrhage. I usually feel that most of this is traumatic.

In the dense scar area there are spaces which have contained fatty acid crystals.

SUMMARY

Following the combined study of histories, gross specimens and microscopic slides over a period of ten years, the opinion is expressed that a large proportion of the nodular thyroid glands, toxic and non-toxic, show the pathological evidences of chronic productive and contractive thyroiditis rather than of adenoma.

The true adenomata in the group follow the pathological conceptions of tumor elsewhere in the body.

A pathological classification is proposed based upon the conception that many of the nodular types of glands are inflammatory and not tumorous.

The incidence of these types under these conditions was studied and tabulated in 1000 cases.

A short clinical classification is offered.

THE KLINE PRECIPITATION REACTION AS AN ADJUNCT TO THE COMPLEMENT-FIXATION TEST IN THE SEROLOGICAL STUDY OF SYPHILIS*

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The status of the tests for the precipitation reaction in the serological study of syphilis has been the subject of extensive and even vehement discussion in the literature of recent years. Originally they were advocated as a substitute for the more laborious and time-consuming complement-fixation test, which the proponents of precipitation tests demanded should be discarded as obsolete. From the ensuing extended investigations have emerged certain rather clear-cut conceptions concerning the status of the precipitation reaction in syphilis.

Briefly recapitulated, these are as follows:

1. The precipitation reaction is completed much more rapidly than the complement-fixation reaction.

2. While technically more simple with regard to the reagents and apparatus required, these tests are not proportionately more simple as far as the mechanism and phenomena involved and, therefore, are equally open to errors of technical origin.

3. Because of the above fact, performance of the Kahn test, as a prototype of precipitation reactions in syphilis, as has been emphasized by many and as later admitted by Kahn, should be left to those properly trained in clinical laboratory methods.

4. The proper reading and interpretation of "border-line" precipitation reactions requires a marked degree of serological training and experience. These tests, therefore, are not suited for infrequent use as office procedures by those whose serological

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training has been superficial or inadequate and whose experience in such matters has been limited or sporadic.

In this connection the report of the League of Nations Conference may be cited, in which it is stated that the conference

"desires to emphasize the fact that, no less than the complement-fixation tests, these flocculation methods are, despite their apparent simplicity, extremely sensitive to the slightest difference in experimental conditions and subject to as many sources of error, in connection both with the execution of the test and the reading and interpretation of the results, so that they must be placed only in the hands of specially trained serologists."

5. The results of numerous and extended investigations have shown that, as could be expected from the inherent principles underlying the production of serological phenomena in syphilis, some sera will react at one time to the precipitation and not to the complement fixation test and vice versa. From this it follows that: (*a*) the two tests supplement one another; (*b*) confirmation of a weak (plus-minus) precipitation reaction is afforded by a coincident positive complement-fixation reaction and vice versa; and, therefore both tests should be used in the serological study of syphilis, one complementing the other and so increasing their joint significance and reliability.

There can be little question that the work of Kahn and his associates has added much to the technical development of the precipitation reaction in syphilis and has stimulated the development of a number of such methods varying in detail. The determination of their suitability as adjuncts to the complement fixation test is of interest and importance.

The purpose of this communication is to present the results of a study of the test proposed by Kline and Young which is not only as rapidly performed as the Kahn test but has the advantage of being technically even more simple.

The present communication supplements and corroborates the conclusions advanced in a previous report upon the same subject and embodies a comparative analysis of 2623 tests, all being routine examinations during 1929 of unselected sera.

The sera were from three sources: (1) Patients from all services in the hospital submitted for routine examination; (2) specimens

from private patients not in the hospital; (3) specimens from the Veneral Disease Clinic of the Municipal Hospital.

Unless the exact nature as well as the reliability of each is known, comparison or analysis of the results of serological procedures is not only unprofitable but may be misleading.

The routine complement-fixation test used in these laboratories is the six-tube quantitative test described by Kolmer the delicacy, reliability, and relative specificity of which in competent hands is no longer a matter of debate.

The Kline test was performed as directed by Dr. Kline after he had very kindly demonstrated his method. The necessary reagents for both tests were made in these laboratories.

Since the original publication Kline has proposed a new antigen as well as "very delicate" and "presumptive" procedures

While it is true that, at times, the clinical diagnosis of syphilis is impossible because of the absence or paucity of clear-cut clinical data and in such instances must rest upon the results of dependable serologic procedures performed by competent workers, it is also true that, whenever possible, serodiagnosis should be confirmed by clinical and therapeutic evidence.

The introduction of so-called "very delicate" and "presumptive" procedures, conveying as it may to the clinician at large a suggestion of absolute specificity incompatible with the mechanism of both complement-fixation and precipitation reactions as these are at present understood, deserves careful consideration. There is a limit to which the delicacy of serological procedures may be advanced without introducing the possibility of false positive reactions the dangerous potentialities of which as regards the patient require no comment.

Moreover, as the purpose of the study was to discuss the suitability of the Kline test under general conditions, the original technic was adhered to and innovations not introduced.

As stated 2623 sera were tested with the following results:

Negative to both tests	2115 or 80 per cent
Negative to Kolmer test	2192 or 83 per cent
Negative to Kline test	2212 or 84 per cent
Positive to Kolmer test	383 or 14 per cent
Positive to Kline test	462 or 16 per cent

While there was thus a very close agreement of both procedures with regard to the negative sera, the discrepancy in both negative and positive reactions, if hastily considered alone, could be accepted as an indication of increased sensitivity on the part of the Kline test. Considered in the light of the extended investigations on precipitation reactions in general, it simply exemplifies what is now widely recognized: that a serum on a single test may be positive to one and negative to the other procedure or vice versa. It thus emphasizes the value of their coincident use.

Moreover, while the Kline test gave seventy-nine more positive reactions than the Kolmer test, forty-five or 57 per cent, of these were plus-minus reactions which, in the absence of definite knowledge of syphilis in the patient in question, must be regarded as without diagnostic significance and as suggesting only the advisability of further study.

The remaining thirty-four positive reactions were clear-cut and indisputable (two plus or more).

In 252 of the positive reactions both tests agreed. While this agreement was absolute with regard to positivity, it was not absolute with regard to the *degree* of positivity, there being numerous Kolmer reactions of definite strength (44440; 44300; 44000, and so forth) coupled with Kline reactions of plus one, plus two, and plus-minus, as well as a number of plus two to plus four Kline reactions coupled with weakly or moderately positive Kolmer reactions (fixation only in the first or second tube).

While it is impossible to evaluate acurately this phase of the study in the absence of equally complete clinical data, the impression gained was that the Kolmer test, if positive, was definitely so, the reaction possessing a definite significance, whereas the Kline test, when weakly positive would have been difficult of clinical interpretation in the unknown case.

It was not uncommon, on the other hand, in the presence of syphilis under treatment, to find the Kline test remaining positive in some degree longer than the complement-fixation test, a phenomenon generally recognized in connection with acceptable precipitation procedures.

The absolute disagreements occurring in 250 sera were as indicated in table 1 which, for brevity's sake, shows only the first fifty sera, anticomplementary sera being omitted.

There were thirty-six, or 1 per cent, anticomplementary reac-

TABLE 1

ILLUSTRATING NATURE OF OPPOSING REACTIONS

KOLMER TEST	KLINE TEST	REMARKS	KOLMER TEST	KLINE TEST	REMARKS
00000	plus 1	Treated	30000	0	Unknown
00000	plus 1	Treated	00000	plus-minus	Unknown
44100	0	Lues	44400	0	Unknown
43000	0	Lues	40000	0	Unknown
44400	0	Unknown	00000	plus-minus	Unknown
42000	0	Unknown	44441	0	Lues
40000	0	Early lesion	40000	0	Lues
0	plus 1	Treated	00000	plus-minus	Treated
0	plus 3	Unknown	00000	plus 2	Treated
40000	0	Donor	00000	plus 3	Unknown
00000	plus 1	Treated	44400	0	Unknown
00000	plus 2	Treated	44400	0	Unknown
44400	0	Spinal lues	01400	0	Primary lesion
44000	0	Unknown	21000	0	Unknown
00000	plus-minus	Unknown	00000	plus 1	Unknown
00000	plus 1	Unknown	43200	0	Unknown
00000	plus 2	Unknown	00000	plus 2	Unknown
44400	0	Unknown	00000	plus 2	Unknown
44440	0	Unknown	44400	0	Lues
04400	0	Unknown	00000	plus 2	Lues
04443	0	Treated	00000	plus 2	Lues
21000	0	Treated	00000	plus-minus	Treated
00000	plus-minus	Treated	00000	plus 1	Treated
40000	0	Unknown	30000	0	Unknown
44400	0	Unknown	44400	0	Lues

tions in all of which Kline test readings were possible, the positive readings in twenty-three sera being shown in table 2.

It may be remarked here that a small number of sera were encountered in which the Kline test could not be read but these were not included in the series.

The data thus summarized suggest that the Kline precipitation

test parallels quite closely the results secured with the Kolmer test and that it is quite suitable as an adjunct to the complement-fixation test in the serological study of syphilis.

The experience accruing from an ever-widening use of the Kolmer test during the past eight years, is quite conclusive that when the Kolmer test is done in strict compliance with Kolmer's directions a definitely positive reaction does not occur in the absence of syphilis or yaws.

The close agreement of the Kline test with the Kolmer test suggests that it also has a high degree of relative specificity. Proof, of this, however, must come largely from clinical evidence and to this end the sera from the Venereal Disease Clinic, for which clinical data is available, are separately considered.

TABLE 2

POSITIVE KLINE READINGS WITH TWENTY-THREE ANTICOMPLEMENTARY SERA

NUMBER OF SERA	KLINE READINGS
2	plus-minus
1	plus 1
4	plus 2
1	plus 3
15	plus 4

Of 514 such sera, 147 were Kolmer positive and 148 Kline positive, an incidence of 28 per cent for each test.

Of the 148 Kline positive sixteen, or 11 per cent, were plus-minus reactions which, in the case of known syphilitic sera, were of definite significance. The majority of the Kolmer reactions in the same sera gave fixation in the first two tubes or, if in one tube only, a reaction seldom below plus three.

Three per cent, or 19 sera, were anticomplementary in all of which Kline readings were definite and readable.

The Kolmer test was negative in 375 sera, or 72 per cent, while 392, or 76 per cent, were negative to the Kline test. These figures do not imply a corresponding lack of delicacy in the Kline test but again illustrate the fact that a serum may be negative to one procedure and positive to another at a particular time.

However, the actual disagreements, which are shown in table 3 are in favor of the delicacy of the Kolmer test.

TABLE 3

DISAGREEMENTS IN KNOWN SYPHILITIC SERA

(Anticomplementary sera omitted)

KOLMER TEST	KLINE TEST	REMARKS	KOLMER TEST	KLINE TEST	REMARKS
00000	plus 1	Treated	44410	0	Treated
00000	plus 1	Treated	00000	plus 2	Treated
00000	plus 1	Treated	00000	plus-minus	Treated
40000	0	Treated	00000	plus 3	Treated
00000	plus 2	Treated	00000	plus-minus	Treated
00000	plus 1	Treated	44400	0	Treated
44400	0	Spinal lues	44443	0	Treated
44000	0	Treated	44400	0	Treated
04400	0	Secondaries	00000	plus-minus	Treated
44444	0	Lues	44400	0	Treated
00000	plus-minus	Treated	44400	0	Treated
00000	plus-minus	Treated	00000	plus 2	Treated
00000	plus 2	Treated	00000	plus-minus	Treated
44400	0	Treated	44300	0	Treated
44400	0	Lesion	44410	0	Treated
00000	plus-minus	Treated	40000	0	Treated
00000	plus 1	Treated	00000	plus 2	Treated
01400	0	Treated	00000	plus 1	Treated
44400	0	Treated	44400	0	Treated
44000	0	Treated	00000	plus-minus	Treated
43200	0	Treated	00000	plus 4	Treated
00000	plus 2	Treated	00000	plus-minus	Treated
00000	plus 2	Treated	44400	0	Treated
00000	plus-minus	Treated	40000	0	Treated
44400	plus-minus	Treated	10000	0	Treated
44000	0	Treated	44400	0	Treated
44100	0	Treated	00000	plus-minus	Treated
00000	plus-minus	Treated	04100	0	Treated
20000	0	Treated	04400	0	Treated
42000	0	Treated	44000	0	Treated
44400	0	Treated	44000	0	Treated
44000	0	Treated	44400	0	Treated
00000	plus 2	Treated	44000	0	Treated
00000	plus-minus	Treated			

SUMMARY

The analysis of a comparative series of 2623 parallel Kolmer complement-fixation and Kline precipitation tests indicates that the Kline technic is a suitable method for the performance of the precipitation test in conjunction with the complement-fixation test in the serological study of syphilis.

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THE REACTION OF THE MENINGES TO THERAPEUTIC SERUM*

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INTRODUCTION

Serum sickness, in its various manifestations, has become a very familiar entity during the past twenty-five years. The reaction of the skin, mucous membranes, joints and lymphatics, following the injection of prophylactic and therapeutic sera has been dealt with at great length in the literature. Kennedy stated that in American literature no mention had ever been made of the effect of injected sera on the structures of the nervous system. In this paper I report certain observations relating to the effect of anti-meningococcal serum on the meninges, briefly review the foreign literature on the subject, and attempt to point out the practical application of the observed facts.

CASE REPORT

Miss M. C., a laboratory technician, was engaged in the routine study of spinal fluid from a patient suffering with meningococcal meningitis. The fluid unexpectedly spurted from a syringe, striking the technician in the face and spattering in the eyes and nose. The danger of the situation was realized and steps taken to prevent the development of infection. Three days later, vague joint pains were complained of and six days after exposure, headache and general malaise were reported. During this day, the temperature rose from 98.6° to 104° and the patient was admitted to the hospital. Headache, projectile vomiting, stiffness of the neck and a positive Kernig sign soon developed. Lumbar puncture revealed a turbid fluid under pressure. It was found to contain 3430 cells and a Gram-negative diplococcus which was later proved by cultural studies to be a meningococcus. The same organism was recovered from

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the blood stream. Antimeningococcal serum was administered by vein and intraspinally. A total of 45 cc. of serum was given intravenously and a total of 230 cc. intraspinally. The product of a well known manufacturer was used in conjunction with serum from the New York City Department of Health, secured through the courtesy of Dr. Josephine Neal. The clinical course of the disease was favorable. The cell count fell to 91 and organisms disappeared from the fluid. The last of twelve daily injections of serum was given on March fourteenth.

Six days later, March 20, there was a recurrence of headache and general malaise. The spinal fluid cell count rose to 391, and meningococci were demonstrated in the fluid. Fifteen cubic centimeters of sera were given intraspinally following the withdrawal of 25 cc. of fluid. Within one hour after the injection, the patient began to be extremely restless and quickly lapsed into unconsciousness. The back gradually became stiff and opisthotonos was very marked. The pupils were irregular and pupillary reactions to light were very sluggish. The preexisting papilledema did not increase. Lateral nystagmus was constantly present and the power of ocular convergence was lost. A high pitched nasal cry was emitted at frequent intervals. There was no cyanosis and no marked variation in pulse, temperature or respiration. The extremities jerked about in continuous, convulsive movements. In semi-rational moments the patient complained bitterly of lancinating headache, pains in the back and especially in the lower extremities. There was complete loss of voluntary sphincter control. Careful examination failed to reveal any involvement of joints or lymph glands. Lumbar puncture was performed. The pressure was approximately the same as that of the preceding punctures (325 mm. of water). The fluid contained 4536 cells but no organisms. No serum was administered. There was no improvement following withdrawal of fluid. The acute symptoms persisted about sixty hours. Four days after the onset of the paroxysm, the cell count had fallen to 291 and the patient was conscious. It was noted at this point that the spinal fluid containing 291 cells was just as turbid as that which had contained 3000 cells. This turbidity was observed for several days and finally disappeared; that is, the degree of turbidity of the fluid and the cell count seemed to be once more in proportion. In an attempt at desensitization, 0.1 cc. of serum was given intravenously. Within an hour the previously described symptoms of coma, convulsions and opisthotonos occurred but in less severe form. Three hours later, these severe symptoms had subsided. There was no further administration of serum by any route. After a prolonged convalescence, the patient recovered entirely and returned to duty.

REVIEW OF LITERATURE

Kennedy reported one case with fulminating cerebral symptoms and five cases of peripheral nerve involvement, following the

administration of serum. The description of his first case coincides closely with my observations. He concluded that the symptoms might have been due either to the toxicity of the serum or to an urticarial edema of the neural tissue. He felt that the latter view was the most tenable.

Goldman recently established the entity of serum meningitis on a firm experimental basis. He referred to another type of meningeal reaction which might be anaphylatic but did not describe the reaction in detail.

Hutinel reported three cases of a severe meningeal type of reaction after intrathecal injection of serum. The number of injections varied from three to twelve and the time between the injections from three days to six weeks. Coma and opisthotonos were pronounced and in all three instances death ensued. Two cases were complicated by tuberculous meningitis. The author felt that the reactions were due to the direct action of the serum on the meninges with the production of urticaria and edema of the meninges.

Delahet reported one case and mentioned five others which exhibited convulsions and coma, the symptoms of which he grouped under the term *choc bulbaire*. In his personal case the reaction followed the intravenous injection of a small amount of serum. The meningeal symptoms recurred at intervals even when no serum was given. The reducing substance of the fluid was much increased. The author regarded the reactions as due to the irritation of the meninges from the formation of precipitins.

Ker described the increased glucose content of the fluid as a diagnostic factor in aseptic meningitis. He did not mention the type of reaction herewith reported.

Longcope referred to cases reported by Grysez and Dupuich and Flandin. He felt that some type of immediate reaction might occur on the surface of the meninges which would give rise to the described symptoms.

Rolleston mentioned emphatically the danger of severe reaction following intrathecal injection. He referred to the work of Netter and Debre, and thought the condition was the same as that described by Dopter under the term, "Seric Meningitis."

Auer reviewed the subject of fatal reactions from intrathecal injections. He felt that the speed of the reported reactions as well as the clinical symptoms indicated increased pressure as the *modus operandi*.

Mackenzie discussed the repeated demonstration of specific precipitins for horse serum in injected individuals. He stated that in severe serum disease, the titer of circulating precipitin was high and those individuals who were insusceptible to serum disease were poor precipitin formers and suggested that the union of antigen and antibody might play a large part in serum reactions.

DISCUSSION

It is evident that the intrathecal injection of foreign serums may result in two different types of reaction. The first is the ordinary response of the meninges to the injection of any foreign substance. It is marked by an increase of total protein and of cell count. The clinical symptoms are not severe and subside quickly. It is apparent that this serum or aseptic meningitis must occur quite regularly in the treatment of tetanus, neurosyphilis and meningitis. Goldman's summary of this subject is excellent.

The type of reaction exemplified by the case herewith reported presents an entirely different and highly individual picture. It was explosive in character and was marked by severe and terrifying symptoms. It was extremely persistent and might even have lead to death. The reaction described does not show any of the usual characteristics of immediate generalized serum reactions in man. There was no evidence of bronchospasm with resulting cyanosis and dyspnoea, nor were there any evidences of splanchnic dilatation and fall of blood pressure. All of the observed phenomena pointed to meningeal irritation of a severe nature as the underlying factor.

One is forced to conclude in a general way that during the process of treatment, a localized allergy involving the tissues of the nervous system alone developed. Further evidence of this fact is supplied by the repetition of the reaction following the injection of a very small quantity of serum (0.1 cc.) intravenously. The amount of serum reaching the nervous system from this

injection must have been very minute, yet it was sufficient to excite the same reaction as produced by intrathecal administration. This interesting phenomenon has been previously observed and described by Chiray as the "reflex sign of pyocephaly."

Rolleston recognized the dangers of intravenous injection following intraspinal medication and stated that even an attempt at desensitization might be hazardous as indeed it proved to be in my case.

The rather peculiar turbidity of the fluid I observed offers field for speculation. The appearance varied somewhat from the yellowish gray spinal fluid which is turbid as the result of the presence of large numbers of cells. The color of the specimen was white, rather than grayish yellow and the cloud did not settle on standing. When first encountered I was surprised to receive reports of low counts from such opalescent fluid. In addition, in spite of a falling count, the opacity of the serum remained rather uniform. In two other cases, I noted this clouding in a slight degree, three days following the administration of serum. These two cases had no evidence of reaction except very severe headache.

I was led by the work of Delahet to investigate the precipitin formation in the spinal fluid of a case of meningococcal meningitis under treatment. A portion of the fluid removed prior to treatment each day was layered with horse serum (tetanus antitoxin) and placed in the incubater at 37.5°C. for eighteen hours. The fluid removed on the fourteenth puncture reacted with the horse serum at the point of contact, as evidenced by the formation of a clear cut white ring about 1 mm. in width. The patient had shown no evidence of anaphylactic reaction but serum therapy was discontinued at this point. The ring formation had entirely disappeared after two more punctures. The ring formation is independent of the protein content as fluids with a total protein as high as 75 mgm. have failed to react with the horse serum.

Manwaring, who worked with dogs sensitized to horse serum, washed the livers of these dogs free of blood by a preliminary perfusion of Locke's solution. They were then perfused with Locke's

solution containing horse serum. The perfusate which had previously been clear suddenly became milky.

In consideration of the above statements, I suggest as a working hypothesis that the gross cloudiness of our spinal fluids, the reaction of one fluid with horse serum and the cloudiness occurring in Manwaring's perfusates, represent a single process, namely, the formation of precipitins in the presence of an excess of precipitinogen (horse serum). I further suggest that the severe meningeal reactions observed by myself and others result from the irritation of the meningeal surfaces by the flocculent precipitate which is thrown down when the spinal fluid comes in contact with the injected horse serum. The precipitins may act merely as mechanical irritants to the meningeal surfaces or it is possible that there is some more specific type of reaction involving the mesothelial cells.

TREATMENT AND PROPHYLAXIS OF MENINGEAL REACTION

In the treatment of the reported case, large doses of epinephrine were used without apparent benefit. The intravenous injection of hypertonic solutions of glucose and repeated spinal drainages were equally ineffectual.

Delahet advises the injection intraspinally of small quantities (5 cc.) of the patient's inactivated blood serum.

It is manifestly important to establish, if possible, some reliable sign of impending meningeal reaction. It has been stated that a rising glucose value in the spinal fluid may be taken as an indication of probable reaction. I feel that this is, however, merely a component of the relatively harmless serum meningitis and bears no relation to the true anaphylactic reaction.

As a more reliable guide, I suggest the overlaying of each specimen of spinal fluid with an equal quantity of horse serum. If a ring appears, at the point of contact, serum therapy should be discontinued unless the indications for administration outweight the possible dangers of reaction. If serum therapy must be continued, the administration of old sera or serum inactivated at 56°C. for forty minutes is advised. The latter procedure is uniformly applied to all sera prepared by the Pasteur Institute and is

believed to account for the lower percentage of serum sickness in France (13 per cent). It is especially important to avoid the intravenous use of serum subsequent to intraspinal administration.

SUMMARY

1. An infection obtained in the laboratory with the meningococcus is reported.

2. A peculiar anaphylactic reaction occurring in the course of serum therapy, and apparently involving the nervous system alone, is described.

3. The meagre literature relating to the action of serum on the nervous system is reviewed.

4. Evidence is offered to indicate that the described reactions are due to irritation of the meninges by the formation of precipitins in the presence of an excess of precipitinogen (horse serum).

5. A method for the detection and prevention of impending meningeal reactions is described.

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THE PRESENT STATUS OF KNOWLEDGE OF CANCER*

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This great mechanical, scientific and publicity age, although it has done much for civilization, has nevertheless failed to eliminate superficiality of knowledge, and snap judgments from enthusiasm. These three factors are obvious in the mental attitude of members of the medical profession and laymen in dealing with the economic problem of cancer. It is natural for all to have an emotional attitude toward this disease which destroys so many men and women in the best and most productive period of life. Naturally we all wish to curtail and eradicate this activity. The problem is not a new one although there is much circumstantial evidence for believing that its importance is increasing.

Every five years for the last quarter of a century I have reviewed the literature in the hope of finding new observations which might be correlated for the purpose of evolving a practical approach to this problem. The abundant literature deals with frequency of the disease, its cause, natural and experimental immunity, the body's natural defensive mechanism, all kinds of diagnostic and prognostic methods and schemes, and many kinds of surgical, radiologic, serologic, dietary, purely physical and chemical methods of treatment. The sources of knowledge are special institutions for research, clinics, hospitals, and private practices all over the civilized world. The literature is too voluminous for any one man to review completely; even the professional abstracters lack completeness in their work.

Recently Woglom reviewed and summarized the experimental data on immunity; he concluded as follows:

* Read before the Ninth Annual Convention of the American Society of Clinical Pathologists, Detroit, Michigan, June 20–23, 1930.

"Immunity to transplantable tumors is a generalized refractory condition which appears to be entirely unrelated to other forms of immunity. No single organ has yet been proved responsible for its elaboration, nor is it affected by physiological conditions such as age or pregnancy. In its acquired form it is neither hereditary nor passively transferable through the body fluids. It seems probable that natural resistance is only the ability to react so promptly and efficiently that a graft is overcome before ever it gains a foothold. The outcome of inoculation is determined by an interplay between the hostility of the host and the proliferative vigour of the implant; hence an absolute immunity does not exist. Resistance is effective during the first few days following the inoculation, but entirely powerless against an established tumor. Nothing may accordingly be hoped for at present in respect to a successful therapy from this direction."

The lay press, in its attempts to present the truth of science, had done much to enlighten the public, to stimulate an interest in early diagnosis and to help eradicate this disease, as it has done with tuberculosis and as it is doing with disease of the heart, lungs, and kidneys. The publicity often has been spectacular and as such has been a great stimulus, although often misleading, especially to patients. Here and there new means of diagnosis and new cures are proclaimed only to recede and then fade into the same obscurity that has characterized panaceas that have appeared in the literature on cancer for centuries.

The medical profession should do more to encourage experiments, trials, and new methods regardless of where and by whom they are made. Professional discredit of newspaper cures may be just as immature and unscientific as the cures and methods themselves. In brief, I know of no specific cures for cancer but I do know of hundreds of patients who once had cancer which has been cured, if the prolongation of useful life beyond the average length of life is considered a cure.

In our enthusiasm for research we have often neglected the good that is being accomplished; we overlook the fact that cancers are being cured and probably prevented every day. I could enumerate many instances of patients who were treated for cancer ten, fifteen and twenty years ago and who are now useful citizens. Add these years to the average age of the patients at the time of treatment and the results are extremely good, considering what would have happened had they not been treated.

After having studied 32,792 patients with cancer I do not feel that the disease is hopeless. In fact I know that it is not hopeless when recognized early, any more than pulmonary tuberculosis, nephritis, cardiac disease, gun-shotwounds, fractures of the legs, hemorrhages and many other common diseases are hopeless. The handling of the cancer problem is quite simple. It rests with the medical profession, a profession which is characterized by traditional ultraconservatism. As long as the medical profession waits for characteristic diagnostic signs and symptoms of cancer just so long will cancer be the same problem it is today. Some of us no longer wait for emaciation, pulmonary hemorrhage, daily rise of temperature, and night sweats before we make the diagnosis of tuberculosis; neither should we wait for palpable masses, cachexia, anemia, lymphatic involvement and metastasis in cases of cancer before making the diagnosis and instituting treatment. The majority of patients with cancer can pass easily the usual insurance examination if they say nothing of symptoms related to cancer; their weight is normal, they are not anemic, their blood pressure is normal, their hearts are normal, they have no albumin, blood cells, or casts in the urine, and no palpable masses. Their condition would not be classified as fit examples of cancer for teaching students in our medical schools and neither would their condition answer the description of cancer in textbooks. Most general pathologists would not see such conditions because the patients have not been subjected to operation or necropsy. Persons with curable cancers are walking about the streets, and there are probably between 3,000,000 and 6,000,000 among us waiting for signs and symptoms before the diagnosis will be made by textbook methods. Figures 1, 2, 3 and 4 illustrate the size of cancers as we see them. It may be seen that it is quite possible to recognize small cancers. Then why is the average cancerous growth so large before radical treatment is instituted? It is of interest that 50 per cent of all cancers of the stomach observed in The Mayo Clinic are inoperable and hopeless, and only half of the remaining 50 per cent are small enough to be removed. Thus only 25 per cent of all patients with cancer of the stomach when seen in the clinic have any possible chance of

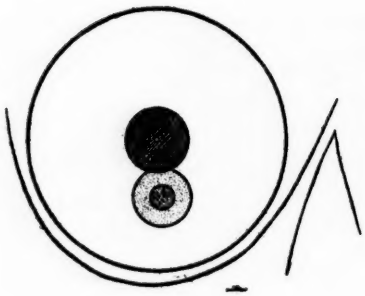

FIG. 1

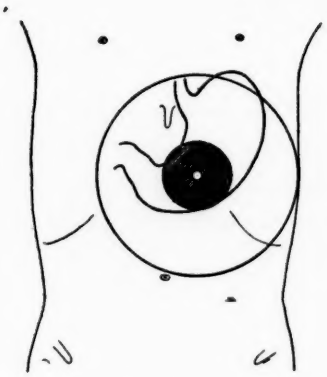

FIG. 2

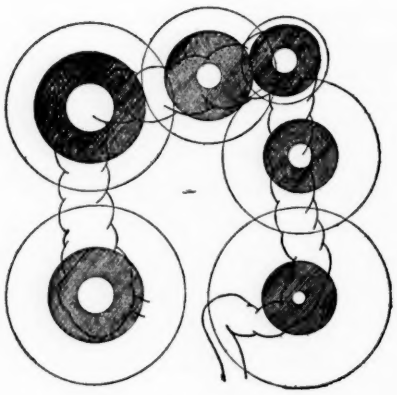

FIG. 3

FIG. 4

FIG. 1. DIAGRAM OF THE BREAST SHOWING THE LARGEST (LARGE CIRCLE), SMALLEST (SMALL CIRCLE), AND AVERAGE SIZE (SHADED CIRCLE) OF SURGICALLY REMOVED CANCERS

FIG. 2. DIAGRAM OF THE STOMACH SHOWING THE LARGEST (LARGE CIRCLE), SMALLEST (SMALL CIRCLE), AND AVERAGE SIZE (SHADED CIRCLE) OF SURGICALLY REMOVED CANCERS

FIG. 3. DIAGRAM OF COLON SHOWING THE LARGEST (LARGE CIRCLES), SMALLEST (SMALL CIRCLES) AND AVERAGE SIZE (SHADED CIRCLES) OF SURGICALLY REMOVED CANCERS IN THE CECUM, HEPATIC FLEXURE, TRANSVERSE COLON, SPLENIC FLEXURE, DESCENDING COLON AND SIGMOID (INCLUDING RECTOSIGMOID)

FIG. 4. DIAGRAM OF RECTUM SHOWING THE LARGEST (LARGE CIRCLE), SMALLEST (SMALL CIRCLE), AND AVERAGE SIZE (SHADED CIRCLE) OF SURGICALLY REMOVED CANCERS

relief and possible cure. The therapeutic results in this 25 per cent are not so bad, considering the late stage of the disease (table 1).

In a series of 200 resected gastric cancers which I studied especially for the relation to postoperative longevity of lymphatic involvement, cellular differentiation, lymphocytic infiltration, fibrosis and hyalinization, I found data in regard to lymphatic involvement as shown in table 2.

TABLE 1

THERAPEUTIC RESULTS

	AVERAGE SIZE OF LESION	PERCENTAGE OF PATIENTS ALIVE AFTER MORE THAN						
		Three years	Five years	Six years	Eight years	Ten years	Eleven years	Fifteen years
	cm.							
Breast with lymphatic involvement	3.92	36.6	21.9		18.9			
		39.2	24.2			13.3		
Breast without lymphatic involvement	2.53	75.6	65		63.9			
		74.6	63			44		
Breast regardless of lymphatic involvement	3.2	44.7					21	
Uterus		62.7					22	7.2
Right half of colon	8					32.3		
Stomach, 1899 to 1909	6.16	29						
Stomach, up to 1911	6.16		22					
Stomach, 1897 to 1917	6.16	38.6	26	14.6				
Stomach, 1897 to 1919	6.16	37.6	25					

Again I wish to emphasize the fact that these are very good results considering that in all of these cases clinical signs and symptoms of cancer were very obvious. They were not the early cancers which are being seen today. The next ten years will show better results because a greater number of small cancers without lymphatic involvement are now being discovered as a result of roentgenology and surgical exploration of conditions such as gastric ulcer, localized chronic mastitis, intestinal hemorrhages,

obscure anemia, and especially unrelieved abdominal distress without specific organic diagnosis.

In 6149 cases of cancer of the breast, stomach, and large intestine, lymphatic involvement was found in 61.2 per cent at operation. These patients were carefully selected for operation, many more than that number having been refused operation.

The point I wish particularly to emphasize is that it is not fair or economically wise to discredit the good results of surgery, radium, and roentgen ray while we are hoping for some specific serologic cure for cancer. If we as a profession forget these good results and lend publicity only to immature and possible but

TABLE 2

RELATION OF LONGEVITY TO LYMPHATIC INVOLVEMENT

LENGTH OF LIFE AFTER OPERATION, MORE THAN	CASES WITHOUT LYMPHATIC INVOLVEMENT	CASES WITH LYMPHATIC INVOLVEMENT
years	*per cent*	*per cent*
1	78.7	50
2	60	25
4	33	14.4
6	21	7.6
8	12	6.7
10	6	0
11	2	0
13	1	0

untried curative means, the layman might be led away from treatments which have already proved their value even under the least favorable circumstances. I wish to emphasize also that early recognizable cancer can be cured and every good surgeon and radiologist knows this. Their only gloom arises when they think of the enormous percentage of cancers which might have been cured had they been seen earlier and had not been held back by some one waiting for the signs and symptoms of cancer which never appear except in the late stages.

CONCLUSIONS

There is no openly demonstrated cure for cancer other than radical removal by operation, or the application of radium or

roentgen ray, or combinations of these. This is an open challenge to those who make other claims. If they accept the challenge and openly demonstrate their results to be better than those I have mentioned then we shall acknowledge gladly their great value.

We should encourage research and be open minded even in the face of doubt but we must do everything possible to keep the public free from false hopes. We should lend every effort to our newspaper friends in their attempts to give valuable scientific facts to the reading public; we should help them decide fairly just what is still experimental and should be kept within the confines of the laboratories until the truth has been substantially demonstrated before scientific bodies.

EDITORIAL

American Journal of Clinical Pathology

For several years, the Executive Committee of the American Society of Clinical Pathologists has studied the possibility of publishing an official journal for the Society. During this period many propositions have been considered, investigated and abandoned. Through an arrangement with The C. V. Mosby Company and Dr. Warren T. Vaughan, the Editor, the Society's notices and the papers presented at the annual convention have been published in the *Journal of Laboratory and Clinical Medicine.* Relations between this Journal and the Society have been both pleasant and profitable. The Society owes a debt of gratitude to the owners of the Journal.

However, as the Society grew it became evident to the Executive Committee that it would be more advantageous for the Society to own and control its own publication. Accordingly, largely through the efforts of Dr. John A. Kolmer, an arrangement has been entered into with The Williams & Wilkins Company, Publishers of Scientific Journals and Books, for the publication of a bi-monthly journal of about 450 pages per volume per year.

By careful management it will be possible to send the JOURNAL to each member of the Society without an increase in dues. If additional subscriptions can be secured and if sufficient high-grade advertisements are obtained, the JOURNAL can be increased in size.

Although the primary purpose of the JOURNAL is to furnish a prompt outlet for the papers presented at the meetings of the Society and for other papers written by members of the Society, it is not proposed to limit publication to papers of members. Nonmembers of the Society may also submit manuscripts which will be accepted by the Editor if they meet the standards of the Editorial Board and if space is available.

The pages of the JOURNAL will be devoted to original articles dealing with clinical pathology as interpreted in its broadest sense. Contributions dealing with new methods, with comparison of old methods, and with applications of clinical pathology to medicine and surgery will be welcome, as will articles on bacteriology, chemistry, pharmacology and physiology as related to laboratory problems in medicine and surgery. Hence the scope of the JOURNAL will be commensurate with the field of clinical pathology.

In addition, the JOURNAL will publish editorials on current laboratory problems, summarizing and commenting upon important investigations. Lastly, the JOURNAL will present a summary of Society activities, as well as important and significant accomplishments of its members.

Elsewhere in this issue will be found certain rules and regulations relative to the form in which manuscripts are to be sent to the Editor. Coöperation in fulfilling these requirements will result in a saving of expense to the Society which will be reflected in an increase in the size and scope of the publication.

It is, of course, hoped that a large number of papers will be submitted in order that the highest type may be selected for publication in the JOURNAL. Naturally concise short articles are most desirable and in choosing and editing papers this will be kept in mind.

The Editor and the Advisory Editorial Board pray for the hearty support of the members of the Society in this new project and invite comments and criticisms that the JOURNAL may not only assume a position of importance among scientific periodicals but may become outstanding in its field.

T. B. M.

SOCIETY NEWS AND NOTICES

Ninth Annual Convention of the American Society of Clinical Pathologists

June, 1930, Detroit, Michigan

A banquet was held in the Book-Cadillac Hotel in Detroit, Michigan, Saturday evening, June 21, 1930, at seven o'clock. Dr. J. H. Black read the presidential address entitled "Biology of Clinical Pathologists" which will be published in full. Dr. Black introduced Dr. M. T. MacEachern who spoke of the usual activities engaged in by his department of the American College of Surgeons in relation to clinical pathologists and surgeons. This was followed by Dr. N. P. Colwell from the Council of Medical Education.

The Ward Burdick award for the year was made to Dr. H. J. Corper. The awards for the scientific exhibits were made to the following: first award to Drs. E. R. Mugrage and Jones of Denver, Colorado; second award to Dr. T. J. Curphey of New York.

Meeting adjourned at ten o'clock.

Meeting of the executive session was held on Monday morning, June 23, 1930, at nine thirty o'clock. The meeting was called to order by Dr. J. H. Black. Reading of the minutes was dispensed with since they had been previously published. Reports of committees followed.

REPORT OF EXECUTIVE COMMITTEE

WARD BURDICK AWARD

In consideration of the manner of awarding the Ward Burdick medal which was referred to the executive committee at the 1929 annual session, the following action has been taken:

The secretary or chairman of the program committee is to require an abstract

with the title of each paper submitted for the program so that it may be determined whether the paper merits a place on the program or not, and in the second place so that the research committee may have abstracts of all papers on the program before the meeting, enabling them to form some idea of the character of the papers to be read and judged.

Determined that there shall be only one Ward Burdick medal awarded each year and that if there is more than one author, the several names shall be engraved on this medal.

The research committee shall reserve the right to withhold the award during any year in which a paper of sufficient merit is not submitted by the members.

HONORARY MEMBERS

The matter of honorary members has been considered by the executive committee at the suggestion of the president and it is the opinion of the committee that we should invite certain distinguished pathologists to become honorary members. The names of Dr. William H. Welch, Rear Admiral E. R. Stitt and Dr. Louis B. Wilson are mentioned for consideration of the society.

OFFICIAL JOURNAL

Since the two years trial of the society's arrangement with the Mosby Company ends with this session, the executive committee suggests that the matter of the official journal be considered by the publication committee at this time.

FINANCIAL AFFAIRS OF SOCIETY

Motion was made, seconded and carried that it is the sense of the executive committee that the annual expenses of the society are more than is good for it and in consequence the secretary be requested to draw up briefly several schedules as to possible curtailment of various activities with the expenditure of a smaller amount of money and present the same schedules to the incoming executive committee when these schedules are ready for their consideration.

Motion was made, seconded and carried that the stenographic report of the society be eliminated from both scientific and business sessions including the present meeting. This provision is a suggestion that will necessitate all committee reports to be made in writing.

The report of the secretary-treasurer as to the present accounts of the society is considered favorably after a review of the summarized report of a certified accountant.

Motion made, seconded and carried that the account of registry for technicians be carried as a separate account from that of the society as it is expected that the registry will carry its own expense.

F. W. Hartman,
Chairman.

Motion made and seconded for acceptance of above report. Carried.

REPORT OF EDITORIAL COMMITTEE

During the past year the papers submitted were as a whole of much higher quality than ever sent in before. There were a few which did not seem suitable for publication in their present form but a casual glance through the journal will show that almost all the papers presented were published. The papers were published in the January and February issues of the journal which is the fastest publication that these papers have ever had in the history of the society. On the other hand, the papers could have been published much sooner had they been received by the Editorial Committee earlier. The Chairman of the committee received the first shipment of papers on October 21, 1929, and at that time no discussions of the papers were included so that we had to wait more than a month after that before the discussions were in.

With almost no exception, discussions of papers read in meetings are of very little value for publication. It is my feeling that if these discussions are not published that men will discuss the papers more freely and it is needless to say that very few men can carry at their finger tips pertinent facts concerning a variety of subjects which are usually presented at such meetings. I should therefore like to make the following two recommendations:

1. That hereafter the discussions of these papers not be published.
2. That the papers be sent to the office of the chairman immediately after they are read.

T. B. Magath,
Chairman.

The above report was read by the secretary.

The recommendations included within the report were voted upon separately. A motion was made and seconded that in the future, papers presented at the annual meeting shall have prepared discussions and these shall be published with the paper. Informal discussions will be permitted and will be printed only on condition that the discussant requests his remarks be published but must make them in writing and submit them to the secretary the day of the meeting so that no delay will take place for the publication committee. Carried.

Motion was made and seconded for acceptance of report. Carried.

REPORT OF PUBLICATION COMMITTEE

The Publication Committee wishes to report that the book being presented under the auspices of the society is practically completed with the exception of the section under chemistry. The committee feels that in all probability it will be ready for publication by next year and requests that the president appoint a committee to go over the subject matter for acceptance.

J. A. KOLMER,
Chairman.

Motion made and seconded for acceptance of report. Carried.

Motion made and seconded that the publication committee in conjunction with the executive committee be given the broadest possible power in the negotiation for the publication of an official journal. Carried.

REPORT OF PUBLIC RELATIONS COMMITTEE

The problems that this committee has more especially to consider include the relations of this society with those other societies and associations which have in part to do with the function of the clinical pathologist. There are also to be considered our relations to public health, hospital, private and commercial laboratories and laboratory technicians.

Some of the members, as your official representatives, have during the past year attended meetings of the American College of Surgeons, American College of Physicians, American Public Health Association and the Council on Medical Education, Licensure and Hospitals.

There appears to be, officially, an endeavor to coöperate with us and aid in improving the status of the clinical pathologist. In certain localities the cooperation between clinical pathologists themselves and between clinical pathologists and the above named organizations is enviable. It is hoped that ultimately this coöperation will extend to all parts of the United States. However, these organizations do not always exactly understand our position. For example we offer the reply of the American Medical Association to the request sent as a result of a resolution passed by the society at the Portland meeting, that clinical pathologists be not solicited for advertisements in the American Medical Association as they should be considered under the same code of ethics as other practicing physicians. Dr. West writes, "that the judicial council of the American Medical Association does not regard it unethical for clinical pathologists to advertise." We believe that if we try to look at it from a broad view we will realize that individually we are practicing physicians, but collectively laboratories are institutions and in the same position with relation to the medical profession as private hospitals are to the public, and there seems to be no objection to hospitals placing advertisements and stating the names of their staffs. The question as to whether we are to consider ourselves from this standpoint or not remains for the society as a whole to decide.

PUBLIC HEALTH LABORATORIES

Our relations and attitude toward public health laboratories continue to be undecided. We, as a representative organization, should continue to oppose whole-heartedly the methods by which these laboratories are encroaching on private laboratory work. Although it may be only when we can get the backing of the general practitioner and various organizations that we will be able to accomplish anything, still we should continue asserting that State or municipal Boards of Health should not do work that lies outside of strictly preventative medicine and that no examinations should be made on any but those who cannot afford to pay. The State, laymen and practicing physicians apparently do not regard it in the light that we do and they cannot be driven. This situation may be improved by education. All that we can expect is a fair opportunity to get the physician who desires laboratory examinations to realize that it is to his credit to give a patient who can afford to pay for it, laboratory examinations and advice that are purchased and not furnished free. When a practitioner wants consultation on a pay patient, he does not expect nor does the consultant expect to furnish it free. He does not call in a consultant who specializes in the care of free patients, but one who has made a name for himself and has a right to command a commensurate fee. So it should be with clinical pathologists.

HOSPITAL LABORATORIES

More and more hospitals are improving in the laboratory service furnished. There is a continuing demand for clinical pathologists to take control of hospital laboratory services. In most places clinical pathologists have some connections with one or more hospitals and the main demand is for more clinical pathologists to direct hospital laboratories. Unfortunately, in some hospitals, technicians are substituted with some member of the clinical staff figuring as head of the laboratory. In the smaller cities and towns which cannot support private laboratories, hospital laboratories necessarily are called upon to do outside work. In the larger cities where there are and rightfully should be private laboratories, we should be opposed to hospital laboratories doing outside work and especially at hospital prices on the ground that hospitals as institutions are competing with us as physicians practicing our specialty. Further, in doing this the hospitals are commercializing the services of their clinical pathologist by competing unfairly with clinical pathologists who operate private laboratories. Those hospitals doing outside laboratory work should be as carefully checked and inspected as outside private laboratories. The system of inspection in effect in New York State should be adopted by all States.

Here we wish to bring up an important point in regard to the comparison of fees that are charged by hospital and private laboratories. Through the county medical societies in any community the laboratory fees should be so fixed that the hospital should have no right to underbid a private laboratory for

laboratory services. This is a growing evil and a menace to the clinical pathologists who hold hospital positions as well as those engaged only in private work. The fact is that some hospitals are reversing their age-old status as an adjunct to the physician in treating the illnesses of mankind to that of commercial institutions in active competition with more than one specialty in medicine. In many hospitals that may otherwise be considered ethical, there is a deplorable cutting of laboratory rates which is unfair to outside competition. We have no complaint to make of pauper patients, but of the pauperizing of patients by public health and hospital laboratories.

We have had several complaints in regard to this. It is the opinion of the committee that steps should be taken by the society so that certain minimum fees may be adopted for laboratory services. We cannot, however, recommend a definite fee that would suit all parts of this country but minimum fees can be recommended and steps be taken to bring them to the attention of all concerned.

It is the opinion of the committee that in addition to all the private laboratories, hospital and public health laboratories should have a proper rating as to their efficiency and standing. We have gone on record as approving and offering our coöperation to the American Medical Association in the classification of laboratories. Like all such beginning undertakings as in classifying medical schools and hospitals, there are bound to be mistakes made. We may be assured that before long this classification will bear excellent results; just as it has done in the raising of a standard of medical schools and hospitals. If the attempt at hospital standardization had not made the progress it has, the demand for clinical pathologists would not be as great as it is now.

We should also be in touch with the Committee on the Cost of Medical Care, to present our views in regard to laboratory cost for the patient, and the income derived by the clinical pathologist from his profession.

LABORATORY TECHNICIANS

We should realize that competent laboratory technicians are as essential to clinical pathologists as nurses are to a hospital. Laboratory technicians should only be employed under the supervision of one competent to direct and check up on every detail of their work. If nurses took over the care of the sick without being under the direction of a physician, the practicing physician would loudly complain. In many cases technicians are employed by those who are incompetent to direct and supervise the accuracy of their work. Therefore, we should condemn the employment of technicians in laboratories of physicians, commercial or hospital laboratories where they are not under the supervision of a clinical pathologist. This could be done through the control of technician registration.

F. B. Johnson,
Chairman.

(Report read by Dr. B. W. Rhamy.)
Motion made and seconded for acceptance of report. Carried.

REPORT OF SERVICE BUREAU

The Service Bureau of the American Society of Clinical Pathologists was organized for the purpose of bringing in touch those members of the society seeking a change in location and institutions desirous of securing the services of competent men of this specialty to direct their clinical laboratories.

The Service Bureau Committee reports progress in its activities. It has received communications requesting aid in obtaining clinical pathologists and has notified members seeking new surroundings of these various opportunities. It is gradually becoming an important and necessary function of the American Society of Clinical Pathologists.

H. J. CORPER,
Chairman.

Motion made and seconded for acceptance of report. Carried.

REPORT OF RESEARCH COMMITTEE

Your Research Committee wishes to report a considerable progress in combined work, in that this year fifty-nine questionnaires were returned with details on many extremely interesting cases. The summary of these cases was taken up in discussion at the Symposium on Agranulocytosis and will be published in full in the JOURNAL. The subject was chosen in order that by thorough discussion of the problem a better understanding of exceptional hematological cases might be obtained. Many of the cases reported were lacking in features which were essential to a proper diagnosis. By a thorough threshing out of this interesting subject, it is expected that our own membership will be more able to handle such cases in the future.

It is interesting to note that in the questionnaires returned, 137 cases of undulant fever had been diagnosed before July, 1929, and by the same men from 1929 to 1930, 111 cases. The agglutinin titer of the blood in these cases averaged 1:320 and 1:640, with some higher and only one man reporting lower values. Blood cultures have been positive in eleven cases, one man reporting 103 cases for both years had seven positives and four other scattered cases were positive out of the total series of 248 reported. This corresponds very well with the similar studies conducted by the New York State Association of Public Health Laboratories in which less than 5 per cent of the cases yielded positive blood cultures.

Apparently our membership had little inclination to try to duplicate L'esperance's work on Hodgkins' disease because only one member reported injection of chicken and this experiment was inconclusive. Your chairman can report two entirely negative cases and can quote also six negatives by Esmond Long of the University of Chicago.

In regard to the Ward Burdick Medal, we regret that no papers were received for perusal by the committee by the appointed date. Apparently the method we chose for selection of the winner was not the proper one. However, your committee does not feel discouraged in the matter since many other societies have the same problem. We hope that a modified plan made at the meeting of the executive committee will settle the problem for future years.

Some members of the committee feel that it would be a good plan to consider problems for joint study a few years in advance, so that definite plans can be drawn up for all the members to follow and material from the various parts of the county will be comparable. Such a plan particularly is apropos in the study of vaccines and vaccine therapy as suggested by Dr. Black. This work we feel should be carried on for more than a year; particularly new cases should be considered following a certain set plan and specifications. This is being done by the committee on vaccines.

We suggest that the subject of agranulocytosis or blood conditions associated with marked leukopenia be studied during the next year, and forms regarding details necessary for complete study of cases be sent to the members as soon as possible if this subject is chosen.

We thank the President and Secretary for their most earnest coöperation and help, and also the other members who have reported their cases or given help in other ways.

A. G. Foord,
Chairman.

Motion made and seconded for acceptance of report. Carried.

REPORT OF SCIENTIFIC EXHIBITS COMMITTEE

The Scientific Exhibits Committee made a distinct effort throughout the year to obtain as large a number of exhibitors as possible. This was accomplished by circular letters to the membership at large and by personal appeal. We were discouraged however, the net result being two additional exhibitors to the original voluntary exhibitors.

We believe that the offer of awards by the executive committee was useful in stimulating good work. However, the task of choosing the winners was decidedly difficult. The first award went to Drs. E. R. Mugrage and Jones of Denver, Colorado and the second award to Dr. T. J. Curphey of New York, New York.

We thank the officers for their coöperation in our work.

We believe that the obtaining of scientific exhibits should be given sincere attention, and that the question of scientific exibits should be a major part of every convention.

There are no recommendations to be offered.

C. I. Owen,
Chairman.

Motion made and seconded for acceptance of report. Carried.

REPORT OF NECROLOGY COMMITTEE

Whereas, we have lost by death two of our members, Dr. George D. Fussell and Dr. Annymarea P. Saunders, be it resolved that we express our sincere sympathy to the families of these two departed colleagues, and that the obituaries of Dr. Fussell and Dr. Saunders be published in the official journal of the American Society of Clinical Pathologists.

OBITUARIES

Dr. George D. Fussell died at the Clearfield, Pennsylvania Hospital, November 30, 1929 after a brief illness at the age of forty-one years. He was the son of Dr. M. Howard Fussell, Professor of Applied Therapeutics at the University of Pennsylvania Medical School. Dr. George Fussell became associated with the Clearfield Hospital in 1921 and achieved an enviable reputation as a clinical pathologist.

Dr. Annymarea Petersen Saunders died of pneumonia, January 1, 1930. She was born in 1888, graduated from the University of Iowa, College of Medicine in 1912, and licensed to practice medicine in Illinois in 1915. She was ably prepared to practice her specialty, and was formerly in charge of the clinical laboratories and x-ray laboratories at the University Hospital, Chicago, Illinois. From 1921 until the time of her death she was employed as clinical pathologist for the State Psychopathic Institute at Chicago, Illinois.

A. H. Sanford,
Chairman.

Motion made and seconded for acceptance of report. Carried.

AGRANULOCYTOSIS: RESEARCH COMMITTEE REPORT

A questionnaire was sent all members of the American Society of Clinical Pathologists in 1930, in order to collect information about the frequency of and details about cases of agranulocytosis angina and related blood dyscrasias. Sixty cases were reported, exclusive of those presented by Drs. Rosenthal and Miloslavich at the Detroit meeting. None of the reports were obtained from the larger medical centers. In classifying the cases considerable difficulty was encountered, since full details were not obtainable by any practical type of questionnaire. However, of the entire group thirty-eight can be fairly justly classified as showing agranulocytosis, and a clinical and laboratory syndrome of the Schultz type. The summary is best seen in the tabulation.

Of the thirty-eight cases, eighteen were in males and twenty in females. The ages varied from seventeen to seventy-three years, the average being forty-two.

Collected cases of agranulocytosis

NUMBER	SEX	AGE	NECROSIS			TEMPERATURE	DURATION	OUTCOME	ARSPHENAMIN TREATMENT*	JAUNDICE	HEMOGLOBIN	ERYTHROCYTES	LEUKOCYTES	POLYMORPHONUCLEARS	MONOCYTES	LYMPHOCYTES	PLATELETS	BLOOD CULTURE	AUTOPSY	MYELOCYTES IN MARROW	REMARKS
			Gums	Throat	Anus																
							days				*per cent*			*per cent*	*per cent*	*per cent*					
1	M.	39		Cheek		103 105	?	Died			63	3.6	1,000	9		91		−			Transfusions and salvarsan. Improved
2	M.	60		+		104	8	Died			79	4.0	100 450	0		100		−	+	Not examined	Absence of polymorphonuclears in tissues
3	F.	50		+			14	Died			51	2.8	800	1		99	Normal				
4	F.	50	+			105	14	Died					800 2,800	0 80	5	Normal 15	Normal	−	+		Red femur marrow—polymorphonuclears on last day
5	F.	48	+	+		102 105	9	Died		Slight	53	3.5	700	0		100		*Diplococcus pneumoniae*			Studied two hours before death only
6	F.	64	+	+	+	102	90	Living†			64	3.8	1,360 3,200	4 6	21 7	70 77	120,500	−	+	+	†Died of pneumonia 2 months after recovery from agranulocytosis. Polymorphonuclears and myelocytes in bone marrow
7	M.	25	+				90	Living			80	4.3	2,100 2,800 7,400	17 2 83	9	79 84 17			Living		Recovered
8	F.	58	+	+		100 104	12	Died			75	4.4	600	0		100		−	+		Many ulcers in stomach and gut
9	M.	73		+			7	Died		Slight	92	4.2	890	5		95			+		

10	M.	52	+			101	240	Died				4.5	2,800	0	17	83		−			Two remissions to normal
11	F.	35	+		+	101 106	5	Died		Slight	75	4.0	200	3		97		*Strep. pyogenes*	+	Rare	Terminal pneumonia with absence of polymorphonuclears
12	M.	26	+	+		101 105	8	Died			100	5.2	1,100 240	0 5	16 6	84 87		−			
13	F.	24		+		103	4	Died					1,350	0	0	100		−			Had counts of 8,000 to 12,000 with 60 to 70 per cent polymorphonuclears six months previous
14	M.	56	+	+ (Cheek)		101 104	5	Died					1,400 122	2	44	54		−			
15	F.	26	+	+		102 104	10	Died	+			3.9	350	1	7	91		−			
16	M.	52	+			105	3	Died			95		850	0.5	2	94.5	Normal	*Staph. albus*			Died of pneumonia
17	F.	55	+	+		100 105	3	Died			64 50	3.4 2.7	1,100 430	0 0	8 3	92 97		−			
18	M.	73	+			104	28	Died			78 101	4.4 5.8	2,300 24,800	1 89		99 13					Agranulocytosis followed by terminal infection and leukocytosis
19	F.	26	+			102 105	18	Died		Slight	50	3.5	1,100 960	2 0	56 22	42 78		−			Followed plastic on palate
20	M.	55	+	+		101	4	Died	+				1,050 600	15 10	10 9	75 81		−			Followed arsphenamine and mercury for syphilis
21	F.	52	+	+		103	12	Living					1,600 6,300	2 61	11 3	87 36		−	Living		Treated with transfusions and salvarsan
22	M.	21	+			101 103	21	Living			78 55	4.0 2.9	1,100 2,700	3 8	8 12	88 79		−	Living		Recovery in twenty-one days

Collected cases of agranulocytosis—continued

NUMBER	SEX	AGE	NECROSIS			TEMPERATURE	DURATION	OUTCOME	ARSPHENAMIN TREATMENT*	JAUNDICE	HEMOGLOBIN	ERYTHROCYTES	LEUCOCYTES	POLYMORPHONUCLEARS	MONOCYTES	LYMPHOCYTES	PLATELETS	BLOOD CULTURE	AUTOPSY	MYELOCYTES IN MARROW	REMARKS
			Gums	Throat	Anus		days				per cent			per cent	per cent	per cent					
23	F.	29	+	+		102	8	Died			60	3.2	800	1	8	90					
						103					49	2.9	700	0	5	95		–			
24	M.	57					60	Living					2,800	8							Abscess of jaw. Treated by transfusion and typhoid vaccine. Well thirteen months later
													7,500	64				–	Living		
25	F.	26	+	+		98	100	Died			80	4.1	950	0		100		–	+		Several remissions. Death from pneumonia, with leukocytosis
						105					80		30,500	92	2	6					
26	F.	55		+	+	98	16	Died					700	1		99					Marked involvement of throat
						105							500	0		100		–			
27	F.	30		+		100	7	Living			85	4.4	1,600	4	15	81		–	Living		Infection of tongue following needle prick with recovery in seven days
											84	4.7	4,200	47	1	52					
28	F.	33	+	+		104	10	Living			60	3.2	2,800	12	1	87		–			Infection in mouth following teeth extraction. Recovery
29	M.	28	+	+		102	60	Living	?		85	4.8	1,900	26	9	62		–	Living		Arsphenamin six months before onset. Later recovery after transfusions
30	M.	22	+	+		103	4	Died	+		80	4.2	3,200	3	5	92		–			Sudden onset after one of several arsphenamin injections
											80	4.8	1,800	12	2	81					
31	F.	34	+			101	42	Living			60	3.9	1,950	8	18	74		–	Living		Recovery in six weeks
						104					88	4.0	5,750	64	3	32					

32	M.	17	+	+	+	102 104	8	Died	+	Slight	52 50	3.1 3.0	1,800 1,800	2 2	43 67	55 31	50,000 60,000				Throat involvement followed second arsphenamin. Active secondary lues
33	M.	30	+	+		102 104	18	Died			80 80	4.5 4.4	3,400 3,400	8 0	6 2	86 98	Normal	−			Sister died of aplastic anemia one year later
34	M.	30	+	+		102 104	8	Died	+		90	4.8	600	0	0	100	Normal	−	+		Disease developed in course of arsphenamin treatment
35	F.	55	+	+		103	4	Died			85	4.4	800	0	2	98	Normal	−	+		Died in relapse, following apparent recovery for two weeks
36	M.	24	+	+		103	4	Died	+		78	4.1	600 300	1 0	1 1	98 99	Normal	−	+		Typical onset during sulpharsphenamine treatment
37	F.	50	+	+		102 104	11	Died			85	4.7	2,000 1,800	0	0	100	Normal	Strep. (non-hemolytic)	+		Typical case
38	F.	50	+	+	102	102 104	11	Died			88	4.7	2,000 1,500	0	0	100	244,000	Strep. (non-hemolytic)	+		

* Disease followed treatment.

The gums or throat, or both, were involved in all cases, and a few showed ulcerative lesions about the anus. High temperature, 102° to 104°, was the rule. Nine patients recovered. The duration of the disease varied from three days to eight months, (the latter in a case showing two remissions to normal), the average duration in the fatal cases without remissions being about seven days. Five patients developed the disease following some type of arsphenamine treatment for syphilis, one showing an extremely high monocyte count, similar to cases reported by others. Jaundice was present in only five cases, and in these slight icterus only. The hemoglobin and erythrocyte count was reduced slightly in all cases, but cases with profound anemia were not included. The average leukocyte count was about 1,000 to 1,200, one as low as 350 and one as high as 3,400. The polymorphonuclear leukocytes in seventeen cases, at one examination at least were absent, but on the average a few of these cells were seen. The monocytes varied greatly, lymphocytes forming nearly the entire number of leucocytes in most cases. Reports on blood platelets were made in only ten cases, but undoubtedly most of the cases showed no noteworthy changes. None of the patients showed purpura. Blood cultures were taken in thirty-three cases, and were negative in twenty-eight and positive in five. Bacteriological studies of the mouth lesions showed no constant flora. Autopsies were done on only eleven of the patients dying from agranulocytosis and in these myelocytes were absent or nearly completely so in all of the eight cases reporting bone marrow findings. An occasional case showed a hematologic return to normal and death soon after from an infection associated with an ordinary leukocytic response. In one case in a laboratory worker previous blood counts within a year of the onset of the fatal illness had shown normal findings. One developed a typical agranulocytosis blood picture accompanying an infection of the tongue following a needle prick, one followed removel of teeth and one followed a plastic operation on the palate. In all the autopsied cases lack or absence of granulocytes in infected areas was a striking feature.

For the coming year, 1930–1931, the committee intends to establish a registry for cases of agranulocytosis, purpura thrombocytopenia, and acute leukemia. The members of the society are urged to send in case histories, blood slides, and sections of biopsy and autopsy material. When sufficient material is on hand, it is to be used as a loan collection, the details of management to be arranged later.

Research Committee:
A. G. Foord, *Chairman*,
A. H. Sanford,
F. E. Sondern,
W. M. Simpson,
W. T. Cummins.

REPORT OF BOARD OF CENSORS

The following have been approved by the Board of Censors for membership in the American Society of Clinical Pathologists:

William C. Black	Foster M. Johns
Emil Bogen	Gay B. Kim
Rigney D'Aunoy	Margaret M. Loder
Norbert Enzer	Walter B. Martin (associate)
Joseph W. Jackson	Bernhard Steinberg
Howard M. Jamieson	Douglas R. Venable

Three names were held over for reconsideration during the next year.

Seven names were rejected.

The executive committee submitted the names of Rear Admiral E. R. Stitt, Dr. William Welch and Dr. L. B. Wilson for honorary membership in the society and they have been approved.

F. H. LAMB,
Chairman.

Motion made and seconded that the report be accepted and that those approved be admitted to the society. Carried.

AMENDMENTS TO THE CONSTITUTION AND BY-LAWS

CONSTITUTION

ARTICLE V

Section 5 (addition):

Suspension or expulsion from membership in the Society shall be by three-fourths vote of those members present and voting at a regular executive session.

BY-LAWS

ARTICLE VIII

Section 2 (change):

It shall be deemed unethical for members to publish objectionable laboratory advertisements in any form whatsoever. The Board of Censors to act as judges in the matter, the members having privilege of appeal to the Society at a regular executive session.

Section 3 (change):

It shall be considered unethical for a member to lend his name for publication in any laboratory advertisement or announcement, which violates the Code of Ethics. The borrowing of names of other physicians, scientists or laymen, on the basis of an occasional service or consultation, for purposes of advertising or to sanction the work of a laboratory is misleading and unethical.

Section 4 (addition):

Any system of secretly dividing or rebating fees for laboratory services shall be considered unethical.

Motion made and seconded for the adoption of the above amendments. Carried.

ELECTION OF OFFICERS

The nominating committee presented the names of the following:

President-elect: H. J. Corper
Vice-President: C. I. Owen
Secretary-Treasurer: A. S. Giordano

The candidates presented by the nominating committee were accepted unanimously.

Dr. Giordano then presented his resignation from the executive committee since the secretary-treasurer is or should be an ex-officio member of the executive committee, and he felt that this vacancy should be filled by another member. Resignation accepted.

The other names presented by the committee were:

Executive Committee

J. H. Black	3 years
C. E. Roderick	3 years
F. E. Sondern	2 years

Board of Censors

W. E. King C. W. Maynard

Board of Registry of Technicians

R. W. Hammack	3 years
W. G. Exton	3 years

The above candidates were accepted unanimously.

The members retiring from the committees were:

Executive Committee: W. G. Exton and A. S. Giordano
Board of Censors: R. Ottenberg and C. H. Manlove
Board of Registry of Technicians: W. Thalhimer and E. S. Maxwell

Note: Since the above elections Dr. Exton has requested that he be replaced by some other member on the Board of Registry of Technicians. President Lynch has chosen Dr. M. W. Lyon, Jr., to fill the vacancy.

REPORT OF THE BOARD OF REGISTRY

It gives me pleasure to report to you that the Registry of Technicians during the past year has gone forward with considerable success. Over four hundred laboratory technicians have been given certificates from our Registry.

It is gratifying to note the numerous letters of appreciation and comments that we receive from the licentiates who highly prize this testimonial of their qualifications and feel that their status is thereby greatly elevated.

The members of the Board of Registry are grateful to the colleagues in our Society who have been instrumental in calling the work of the Registry to the attention of their laboratory personnel.

The importance of the technician in the general hospital scheme and care of the sick is now universally recognized. At the last meeting of the Council of Medical Education and Hospitals, held under the auspices of the American Medical Association, in February, the subject of technicians was discussed by members of the Board of Registry.

The progress of the Registry of Technicians has been greatly strengthened by the friendly cooperation and encouragement of the American College of Surgeons. Dr. Malcolm T. MacEachern and his aides have been pointing out to the hospitals they visit the desirability of registering their laboratory technicians under the standards of the American Society of Clinical Pathologists.

The Registry has in quite a number of instances been of service to the members who have availed themselves of our Placement Bureau and obtained competent technicians on short notice.

One of the functions of the Registry is the supervision of schools for technicians. The work this year has been confined to collecting data from the application blanks that were sent out to various medical schools and universities having a course for technicians. We are not yet prepared to give the results of the survey of schools.

Judging by the progress made by the Registry in the two years of its existence, we may confidently predict for it a permanence and stability which will prove of benefit to the technicians as well as to the clinical pathologists.

Board of Registry
PHILIP HILLKOWITZ, *Chairman.*
KANO IKEDA,
ALVIN G. FOORD,
C. Y. WHITE,
E. S. MAXWELL,
WILLIAM THALHIMER.

EXECUTIVE COMMITTEE MEETING

The meeting of the executive committee was held in the Book-Cadillac Hotel, Monday afternoon, June 23, 1930, at one o'clock.

Dr. J. H. Black was appointed chairman of the executive committee by President K. M. Lynch.

Dr. A. H. Sanford brought up the question of publication of the journal. Dr. J. A. Kolmer suggested that he be permitted to negotiate with the Williams and Wilkins Company in regard to the journal. This was moved and approved.

Meeting adjourned.